Author’s response to reviews

Title: Advanced Biliary Tract Carcinomas: A Retrospective Multicenter Analysis of First and Second-line Chemotherapy

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Author’s response to reviews: see over
Dear Editorial Committee,

We are very pleased to submit our revised manuscript written by Fiteni F. et al. entitled “Advanced biliary tract carcinomas: a retrospective multicenter analysis of first and second-line chemotherapy”.

Editorial, as well as reviewer comments were taken into account in this revised manuscript. Please find below a point-by-point response to referees’ comments. Changes were performed in red in the revised manuscript.

Reviewer’s report:

Reviewer 1:

Fiteni et. al reviewed 64 patients with advanced biliary tract carcinomas as a retrospective multicenter analysis in first and second-line setting. The aim of the study was to assess the efficacy and safety of different platinum-based chemotherapies administered as first line in
patients with aBTC. Although this is not a randomized clinical trial, the clinical results in a rare disease like aBTC has a merit to be published. However in a retrospective like this, it cannot make any conclusion about the hypothesis rather the clinical results are generally hypothesis generating.

1. Statistics section should be simplified to show primary and secondary end-points. I would remove the univariate and multivariate analysis of the other factors in this setting (N=64) with two different chemotherapy and 5 different variables. Such analysis does not have any merit in this setting.

We are aware of the limitations of our retrospective study with limited number of patients and comparing two different chemotherapy regimens in two different period of time. However, limited data exist in this field and we think that our observations, even though non conclusive, can help clinicians in case of patients “not fit” to standard cisplatin-gemcitabine regimen, and for future trials.

Statistical analysis section was simplified following reviewer’s recommendations:

**Statistical analysis** section (page 6):

“The primary end point was the treatment efficacy of first line chemotherapy in terms of OS. Secondary endpoints were PFS and toxicity of the GEMOX and Gem/Carb regimens as first-line therapy, treatment efficacy of second-line chemotherapy in terms of OS and PFS, and evaluation of possible prognostic factors. OS was defined as the time from the first chemotherapy to death from all causes. PFS was defined as the time from the first chemotherapy to the earliest date of disease progression (local, regional, distant and second cancer), death (from all causes) or data cut-off (from all causes). OS and PFS were estimated using Kaplan Meier method and described by median with 95% Confidence Interval (CI).
Survival curves were compared using log-rank test.

All categorical data were compared using Fisher’s exact test or χ² test.

Univariate Proportional hazards Cox models were used to estimate Hazard ratio with its 95% CI and to select potential prognosis factor for OS and PFS. All variables with p < 0.2 observed in univariate analysis were included in multivariate analysis. The following variables were studied: age, ECOG-PS, tumour location, prior surgical resection, number of metastatic sites, and treatment. Safety was reported for all subjects who received at least one dose of chemotherapy.

P value of 0.05 or lower was considered as statistically significant.

The data were analyzed by using PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.” was replaced by:

“The primary end point was the treatment efficacy of first line chemotherapy in terms of OS. Secondary endpoints were PFS and toxicity of the GEMOX and Gem/Carb regimens as first-line therapy, treatment efficacy of second-line chemotherapy in terms of OS and PFS, and evaluation of possible prognostic factors. OS was defined as the time from the first chemotherapy to death from all causes. PFS was defined as the time from the first chemotherapy to the earliest date of disease progression (local, regional, distant and second cancer), death (from all causes) or data cut-off (from all causes). OS and PFS were estimated using Kaplan Meier method and described by median with 95% Confidence Interval (CI).

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metastatic sites, and treatment.

Safety was reported for all subjects who received at least one dose of chemotherapy.
The data were analyzed by using PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.”

2. Results section

Showing survival data in the two groups and safety data are presented nicely but I would remove the univariate and multivariate analysis section.

Result section was modified following reviewer’s recommendations, as well as in abstract and discussion sections. Corresponding tables were removed:

**Result section** (page 7)

“Twenty patients received Gem/Carb regimen. Mean age was 62 years (range 34-78) with 9 males and 11 females (ratio, 0.82). Fourteen patients (70%) presented ECOG-PS of 0-1 at diagnosis. All 20 patients were dead at the time of analysis. (Table 1) There were 1 CR (5%), 1 PR (5%), 6 SD (30%) and 12 (60%) progression disease (PD). Median OS was 4.8 months (95%CI, 3.7 to 5.8) (figure 1), and median PFS was 2.5 months (95%CI, 2.1 to 3.7) (figure 2). One patient who had primarily unresectable disease underwent curative-intent surgery after chemotherapy. PFS in this patient was 11.9 months.

Forty-four patients received GEMOX regimen. Mean age was 66 years, (range 47-84 years) with 29 males and 15 females (ratio, 1.93). Thirty-four patients (78%) presented ECOG-PS of 0-1 at diagnosis. Eleven patients were alive at the time of analysis with a median follow-up of 35 months. (Table 1) There were 3 CR (7%), 5 PR (11%), 9 SD (20%) and 27 PD (61%). Median OS was 10.5 months (95%CI, 6.4 to 14.7) (figure 1), and median PFS was 3.7 months
In 2 patients the tumour became resectable after chemotherapy. Their PFS was 13.3 and 14.3 months.

Over 64 patients treated with platinum/gemcitabine combinations as front-line regimen, 8 (13%) had a median OS > 24 months.

In univariate survival analysis, chemotherapy and prior surgical resection were statistically significant for PFS (Table 2) while chemotherapy and ECOG-PS were statistically significant for OS (Table 3). In multivariate analysis, GEMOX regimen was the only statistically significant prognostic factor for PFS (HR, 0.51; 95%CI, 0.28 to 0.93; p=0.01) (Table 2) and OS (HR, 0.52; 95%CI, 0.29 to 0.94; p=0.03) (Table 3).” was replaced by:

“Twenty patients received Gem/Carb regimen. Mean age was 62 years (range 34-78) with 9 males and 11 females (ratio, 0.82). Fourteen patients (70%) presented ECOG-PS of 0-1 at diagnosis. All 20 patients were dead at the time of analysis. (Table 1) There were 1 CR (5%), 1 PR (5%), 6 SD (30%) and 12 (60%) progression disease (PD). Median OS was 4.8 months (95%CI, 3.7 to 5.8) (figure 1), and median PFS was 2.5 months (95%CI, 2.1 to 3.7) (figure 2).

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Median OS was 10.5 months (95%CI, 6.4 to 14.7) (figure 1), and median PFS was 3.7 months (95%CI, 2.4 to 5) (figure 2). In 2 patients the tumour became resectable after chemotherapy. Their PFS was 13.3 and 14.3 months.

Over 64 patients treated with platinum/gemcitabine combinations as front-line regimen, 8 (13%) had a median OS > 24 months.
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Abstract section (page 3)

“With GEMOX regimen, median progression-free survival (PFS) was 3.7 months (95%CI, 2.4 to 5) and median overall survival (OS) was 10.5 months (95%CI, 6.4 to 14.7). Disease control rate (DCR) was 38.6% (3 complete response (CR), 5 partial response (PR), 9 stable disease (SD)). The main toxicities were thrombocytopenia (2% grade 3) and peripheral neuropathy (20% grade 2 and 7% grade 3).

With Gem/Carb regimen, PFS was 2.5 months (95%CI, 2.1 to 3.7) and OS was 4.8 months (95%CI, 3.7 to 5.8). DCR was 40% (1 CR, 1 PR, 6 SD). The main grade 3/4 toxicities were haematological: anaemia (45%), thrombocytopenia (45%), and neutropenia (40%). GEMOX regimen was the only statistically significant prognostic factor in multivariate analysis for PFS (HR, 0.51; 95%CI, 0.28 to 0.93; p=0.01) and OS (HR, 0.52; 95%CI, 0.29 to 0.94; p=0.03).” was replaced by:

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haematological: anaemia (45%), thrombocytopenia (45%), and neutropenia (40%). GEMOX regime was the only statistically significant prognostic factor in multivariate analysis for PFS (HR, 0.51; 95%CI, 0.28 to 0.93; p=0.01) and OS (HR, 0.52; 95%CI, 0.29 to 0.94; p=0.03).”

Discussion section (page 10)

“In aBTCs, Williams and al conducted a phase II trial (gemcitabine 1000mg/m² and 8 and carboplatin AUC 5 Day 1, every three weeks) and 48 patients were consecutively included with a median OS of 10.6 months (95%CI, 8.8 to 14.2).[19] Our cohort did worse with the same treatment schedule. Even though 20 patients are certainly underpowered to estimate OS, it was only 4.8 months (95%CI, 3.7 to 5.8). Even though there are clear limitations in this small retrospective and not matched case-control study, GEMOX regimen was the only independent prognostic factor for PFS and OS in the multivariate analysis.” was replaced by:

“In aBTCs, Williams and al conducted a phase II trial (gemcitabine 1000mg/m² and 8 and carboplatin AUC 5 Day 1, every three weeks) and 48 patients were consecutively included with a median OS of 10.6 months (95%CI, 8.8 to 14.2).[19] Our cohort did worse with the same treatment schedule. Even though 20 patients are certainly underpowered to estimate OS, it was only 4.8 months (95%CI, 3.7 to 5.8). Even though there are clear limitations in this small retrospective and not matched case-control study, GEMOX regimen was the only independent prognostic factor for PFS and OS in the multivariate analysis.”

3. Safety

Since this is a retrospective study; would elucidate how the safety information is collected; medical chart review or electronic data capture.
Safety information was collected using both electronic and paper version of patients’ medical records as well as pharmacy records about adverse and severe adverse events related to each cycle of chemotherapy.

Information recover was performed using predefined data extraction form. Concerning safety, predefined all grade haematological and non-haematological toxicities were recovered based in CTCAE v4.0. “Other toxicity” section was added in data extraction form to recover rare non-predefined toxicities. Two authors (FF and SK) validated the final information.

4. Discussion

As authors eluded in the introduction, the standard of care for fit patients in this setting is gem+cis; so discussion should focus on why gem+ox was used in the institution and what are comparable difference in the two regimen.

Evidence based approach should recommend Gem+cis and the arguments of the authors insisting GEMOX based on a retrospective study is not very compelling.

Authors mention 16 patients with poor PS; the clinical outcome on these patients would be helpful to argue in favor or GEMOX or safety profile of GEMOX can be compared to the ABC study.

Gem/CDDP regimen became standard since 2010 based in a well-designed phase III ABC-02 trial. Our respective study analysed patients treated between 1998 and 2010. Before ABC-02 trial results, Gem/CDDP regimen was not considered as a standard regimen in our institution and no patient was treated by this regimen during this period.

As recommended by the reviewer, we added the safety profile of ABC-02 study in the discussion section. We also changed our conclusion to make more clear that the standard
regimen remains Gem/CDDP, and that GEMOX regimen could be an alternative for unfit patients to CDDP due to its favourable safety profile.

**Discussion section (page 9,10)**

“In our study, we used biweekly GEMOX regimen. However it is slightly different to André’s one. Both, gemcitabine and oxaliplatin are administered at day 1 with gemcitabine preceding oxaliplatin. Our result, based in non-selected patients, showed an OS of 10.5 months. Even though our cohort has several limitations like small number of patients, retrospective analysis, and no control arm, this OS result is still encouraging since there were more ECOG-PS 2 patients and higher median age than randomized or well designed phase II trials. The treatment was well tolerated. The main toxicity was peripheral neuropathy observed in 59%. Oxaliplatin was stopped in only 3 patients for grade 3 adverse events, and no grade 4 was reported.

Gem/Carb combination was successfully assessed in several phase III trials for tumours from different sites (e.g., lung, and bladder cancers).[16-18] In aBTCs, Williams and al conducted a phase II trial (gemcitabine 1000mg/m² and 8 and carboplatin AUC 5 Day 1, every three weeks) and 48 patients were consecutively included with a median OS of 10.6 months (95%CI, 8.8 to14.2).[19] Our cohort did worse with the same treatment schedule. Even though 20 patients are certainly underpowered to estimate OS, it was only 4.8 months (95%CI, 3.7 to 5.8).” was replaced by:

“In our study, we used biweekly GEMOX regimen. However it is slightly different to André’s one. Both, gemcitabine and oxaliplatin are administered at day 1 with gemcitabine preceding oxaliplatin. Our result, based in non-selected patients, showed an OS of 10.5 months. Even though our cohort has several limitations like small number of patients, retrospective analysis,
and no control arm, this OS result is still encouraging since there were more ECOG-PS 2
patients and higher median age than randomized or well designed phase II trials. The
treatment was well tolerated. The main toxicity was peripheral neuropathy observed in 59%.
Oxaliplatin was stopped in 3 patients for grade 3 peripheral neuropathy. Other grade 3
toxicities were rare and no grade 4 was reported. In ABC02 study, more than 70% of patients
presented grade 3 or 4 toxicities in Gem/CDDP arm, and significantly more haematological
toxicities were observed compared to gemcitabine arm.

Gem/Carb combination was successfully assessed in several phase III trials for tumours from
different sites (e.g., lung, and bladder cancers).[16-18] In aBTCs, Williams and al conducted
a phase II trial (gemcitabine 1000mg/m² and 8 and carboplatin AUC 5 Day 1, every three
weeks) and 48 patients were consecutively included with a median OS of 10.6 months
(95%CI, 8.8 to14.2).[19] Our cohort did worse with the same treatment schedule. Even
though 20 patients are certainly underpowered to estimate OS, it was only 4.8 months
(95%CI, 3.7 to 5.8). Grade 3 or 4 toxicities were frequent, including grade 4 haematological
toxicities.”

**Conclusion section** (page 11)

“In conclusion, GEMOX regimen was significantly superior to Gem/Carb regimen in terms of
PFS and OS, and it was the only prognostic factor in multivariate analysis.

At second-line, selective patients may benefit from fluoropyrimidine-based chemotherapy.”

was replaced by:

“In conclusion, one day GEMOX regimen has a favourable toxicity profile and could be an
alternative to standard Gem/CDDP regimen, in particular in unfit patients for CDDP. was
significantly superior to Gem/Carb regimen in terms of PFS and OS, and it was the only
prognostic factor in multivariate analysis.
At second-line, selective patients may benefit from fluoropyrimidine-based chemotherapy.”

Reviewer 2:

Major comment

1. Because current standard regimen is Gem/CDDP, You should describe the reason why you use Gem/Carb in clinical practice settings in introduction. Is there no patients treated with GEM/CDDP regimen in your institutions and hospitals?

This study is retrospective study. Therefore you have treated patients as a clinical practice settings without informed consent of clinical trial using new treatment regimen. It is unethically to treat patients with non-standard regimens in clinical practice settings.

Gem/CDDP regimen became standard since 2010 based in a well-designed phase III ABC-02 trial. Our respective study analysed patients treated between 1998 and 2010. Before ABC-02 trial results, Gem/CDDP regimen was not considered as a standard regimen in our institution and no patient was treated by this regimen during this period.

Based in the best of our knowledge at that time and approved by our multidisciplinary committee, Gem/Carbo regimen was our standard before 2004, and GEMOX regimen thereafter.

We made corrections as suggested by the editor to make it more clear in introduction section

**Introduction section (page 4)**

“Different GEMOX regimens were assessed in several phase II clinical trials with OS no
longer than 12 months. In 2010, a randomized multicenter phase III ABC-02 trial established Gem/CDDP as a standard regimen in aBTC. OS was 11.7 months in favour to combination arm compared to 8.1 months in gemcitabine arm (HR, 0.64; 95% CI 95%, 0.52 to 0.80; P<0.001). However, many cancer institutions continue to use GEMOX as standard regimen because of its easy administration and good tolerance profile. Since 2004, based in existing data, our multidisciplinary committee approved biweekly GEMOX regimen as a standard in aBTC in replacement of former standard, Gem/Carb regimen.” was replaced by:

“Different GEMOX regimens were assessed in several phase II clinical trials with OS no longer than 12 months. In 2010, a randomized multicenter phase III ABC-02 trial established Gem/CDDP as a standard regimen in aBTC. OS was 11.7 months in favour to combination arm compared to 8.1 months in gemcitabine arm (HR, 0.64; 95% CI 95%, 0.52 to 0.80; P<0.001). However, many cancer institutions continue to use GEMOX as standard regimen because of its easy administration and good tolerance profile. Since 2004, based in existing data, our multidisciplinary committee approved biweekly GEMOX regimen as a standard in aBTC in replacement of former standard, Gem/Carb regimen. Before ABC-02 trial results, our multidisciplinary committee approved Gem/Carb combination as standard regimen for aBTC up to December 2004, and biweekly GEMOX regimen thereafter, based in existing data at that time.”

2. Patients number was too small to perform multivariate analysis. I think it is under-powered analysis and it makes results unreliable.

As recommended by both reviewers, we decided not to publish multivariate as well as univariate analysis results of this study.
Minor comments

1. Page 5, Line 2 ###former standard, Gem/Carb regimen.

"Gem/CDDP " is standard regimen.

We made the phrase more clear to avoid confusion

“In 2010, a randomized multicenter phase III ABC-02 trial established Gem/CDDP as a
standard regimen in aBTC. OS was 11.7 months in favour to combination arm compared to
8.1 months in gemcitabine arm (HR, 0.64; 95% CI 95%, 0.52 to 0.80; P<0.001).[13] Before
ABC-02 trial results, our multidisciplinary committee approved Gem/Carb combination as
standard regimen for aBTC up to early 2004, and biweekly GEMOX regimen thereafter,
based in existing data at that time.”

2. Page 7, last line

Ethics committee approved the analysis protocol.

Ethics committees of "All "participated institutions and hospitals?

All 3 hospitals participating in this study belongs to same regional cancer institution, “Institut
Regional Fédératif de Cancer de Franche Comté” as specified in Methods section (page 5). Therefore, we also have only one regional ethics committee, “CPP Est-II” who approved this retrospective study.

Following the editors’ recommendation, we added the name of the corresponding ethics
committee.

Methods section (page 6)
“Ethics committee approved the analysis protocol.” was replaced by:
“After approval by the ethical committee CPP Est-II, the protocol was

3. Page 8, last line
Their PFS was ###
PFS? recurrent free survival? these two patients received resection.

As recommended by the reviewer, PFS was replaced by recurrence free survival (RFS) in the result section

Result section (page 8)
“One patient who had primarily unresectable disease underwent curative-intent surgery after chemotherapy. PFS in this patient was 11.9 months.
Forty-four patients received GEMOX regimen. Mean age was 66 years, (range 47-84 years) with 29 males and 15 females (ratio, 1.93). Thirty-four patients (78%) presented ECOG-PS of 0-1 at diagnosis. Eleven patients were alive at the time of analysis with a median follow-up of 35 months. (Table 1) There were 3 CR (7%), 5 PR (11%), 9 SD (20%) and 27 PD (61%). Median OS was 10.5 months (95%CI, 6.4 to 14.7) (figure 1), and median PFS was 3.7 months (95%CI, 2.4 to 5) (figure 2). In 2 patients the tumour became resectable after chemotherapy. Their PFS was 13.3 and 14.3 months.” was replaced by:
“One patient who had primarily unresectable disease underwent curative-intent surgery after chemotherapy. Recurrence free survival (RFS) in this patient was 11.9 months.
Forty-four patients received GEMOX regimen. Mean age was 66 years, (range 47-84 years) with 29 males and 15 females (ratio, 1.93). Thirty-four patients (78%) presented ECOG-PS of 0-1 at diagnosis. Eleven patients were alive at the time of analysis with a median follow-up of
35 months. (Table 1) There were 3 CR (7%), 5 PR (11%), 9 SD (20%) and 27 PD (61%).

Median OS was 10.5 months (95%CI, 6.4 to 14.7) (figure 1), and median PFS was 3.7 months (95%CI, 2.4 to 5) (figure 2). In 2 patients the tumour became resectable after chemotherapy. Their RFS was 13.3 and 14.3 months.”

As recommended by both reviewers, new English correction was performed.

Finally, as recommended by the editors, corrections have been done to be in conformity to the journal style.