Durvalumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin in advanced biliary tract cancer: a real-world, retrospective, multicenter study.

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ABSTRACT

BACKGROUND: The TOPAZ-1 phase III trial reported a survival benefit with the anti-programmed cell death ligand 1 (anti-PD-L1) durvalumab in combination with gemcitabine and cisplatin in patients with advanced biliary tract cancer (BTC). The present study investigated for the first time the impact on survival of adding durvalumab to cisplatin/gemcitabine compared to cisplatin/gemcitabine in a real-world setting.

METHODS: The analyzed population included patients with unresectable, locally advanced, or metastatic BTC treated with durvalumab in combination with cisplatin/gemcitabine or cisplatin/gemcitabine alone. The impact of adding durvalumab to chemotherapy in terms of overall survival (OS) and progression free survival (PFS) was investigated with univariate and multivariate analysis.

RESULTS: Overall, 358 patients were included in the analysis: 213 received cisplatin/gemcitabine alone, 145 received cisplatin/gemcitabine plus durvalumab. At the univariate analysis, the addition of durvalumab was found to have an impact on survival, with a median OS of 12.9 months versus 11.2 months (HR 0.6, 95% CI 0.4-0.8, p=0.0016) in patients who received cisplatin/gemcitabine plus durvalumab compared to those who received cisplatin/gemcitabine alone. At the univariate analysis for PFS, the addition of durvalumab to cisplatin/gemcitabine resulted to have a survival impact, with a median PFS of 8.9 months and 6.0 months (HR 0.6, 95% CI 0.4-0.7, p=<0.0001) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively. The multivariate analysis confirmed that adding durvalumab to cisplatin/gemcitabine is an independent prognostic factor for OS and PFS, with patients >70 years old and those affected by locally advanced disease experiencing the highest survival benefit. Finally, an exploratory

analysis of prognostic factors was performed in the cohort of patients who received durvalumab: NLR>3 and ECOG PS>0 resulted to be independent prognostic factors in terms of OS and PFS. The interaction test highlighted NLR>3 and ECOG>0 as predictive factors of response to cisplatin/gemcitabine plus durvalumab.

CONCLUSION: In line with the results of the TOPAZ-1 trial, adding durvalumab to cisplatin/gemcitabine has been confirmed to confer a survival benefit in terms of OS and PFS in a real-world setting of patients with advanced BTC.

1. INTRODUCTION

Advanced biliary tract cancer (BTC) remains a big clinical challenge in the oncology field, due to the dismal prognosis and suboptimal response to systemic treatments (1-4). However, in recent years there has been a significant improvement in the therapeutic armamentarium available against this heterogeneous group of diseases, above all thanks to the growing knowledge of its biological substrate. Molecular insights have revealed a number of targetable genomic alterations, including *IDH1* mutations and *FGFR2* gene fusions, with important therapeutic implications and positive results from prospective trials investigating targeted therapies in molecularly selected subgroups of patients with advanced BTC (5-12). Moreover, in 2022 another class of compounds has been introduced in the BTC treatment: immunotherapy. The phase III randomized double-blind placebo-controlled TOPAZ-1 trial investigated the role of the anti-programmed cell death ligand 1 (PD-L1) durvalumab in addition to the chemotherapy backbone cisplatin/gemcitabine in patients with advanced BTC candidate to a first-line systemic treatment (9). This study demonstrated a survival benefit in favor of the combination of durvalumab plus chemotherapy compared to chemotherapy alone, with a median overall survival (OS) of 12.8 months compared to 11.5 months (Hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.66 to 0.97; p=0.021) (13). Following the TOPAZ-1 trial, the combination of durvalumab and cisplatin/gemcitabine has been approved by the United States Food and Drugs Administration (FDA) and European Medicine Agency (EMA) as new first-line standard of care for patients with previously untreated, unresectable or metastatic BTC. Another immune checkpoint inhibitor (ICI) has recently received the FDA approval for the treatment of the advanced BTC: the anti-programmed cell death 1 (anti-PD1) pembrolizumab. In the randomized double-blind placebo-controlled phase III KEYNOTE-966 study, the authors demonstrated a significantly improved OS in patients who received the combination of pembrolizumab plus cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (12.7 versus 10.9 months respectively, hazard ratio 0·83 [95% CI 0·72–0·95], p=0.0034), whereas no statistically significant differences in terms of progression free survival (PFS) were shown (14).

Outside the clinical trial framework, our research group recently evaluated the efficacy and safety outcomes of durvalumab plus cisplatin/gemcitabine in patients with advanced BTC treated at 17 Italian institutions. We

retrospectively enrolled 145 patients who received durvalumab in combination with cisplatin/gemcitabine for unresectable or metastatic BTC in a real-world setting, showing survival outcomes which were consistent with those of the TOPAZ-1 trial (15). In addition, the incidence of any grade adverse events highlighted in our cohort of patients resulted to be in line with those reported in the TOPAZ-1 trial, thus confirming the safety profile and the good tolerance of the combination (15). If results from randomized prospective trials are the only ones which could change the clinical practice, real-world data are crucial in order to confirm trials' results in a more heterogeneous and less selected population.

In the present work we retrospectively compared two cohorts of patients, the first one receiving the previous standard of care (cisplatin/gemcitabine) and the second one receiving the new combination (durvalumab plus cisplatin/gemcitabine), with the aim to evaluate the survival impact derived by the addition of durvalumab to chemotherapy. Furthermore, we performed an exploratory analysis of prognostic and predictive factors of response to durvalumab plus cisplatin/gemcitabine, with the aim of identifying potential prognostic factors.

2. MATHERIALS AND METHODS

2.1. Study Population

The study population included consecutive patients with unresectable, locally advanced, or metastatic adenocarcinoma of biliary tract, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma. Data were prospectively collected from 17 centers in Italy from March 2006 to December 2022. Patients who received treatment before the publication of the TOPAZ-1 results received the previous standard combination of cisplatin 25 mg/m2 plus gemcitabine 1000mg/m2 on days 1 and 8 of each 21-day cycle for up to 8 cycles, according to the ABC-02 trial (16). Patients who received treatment after the publication of the TOPAZ-1 results received durvalumab 1500 mg administered on day 1 of each cycle in combination with cisplatin/gemcitabine; after completion of 8 cycles, patients received maintenance therapy with durvalumab 1500 mg monotherapy administered every 4 weeks until clinical or imaging disease progression or unacceptable toxicity (13). Since durvalumab was not approved by the EMA until December 21, 2022, and it is not yet reimbursed by the Italian Medicines Agency (AIFA), durvalumab was provided free of charge at the request of the treating physician for each individual patient by AstraZeneca Italy as part of an early access program. AstraZeneca Italy had no role in planning this study, collecting, or analyzing patient data.

The present study was approved by local Ethics Committee at each center, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfilled the

Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data.

2.2. Statistical analysis

The primary endpoint of the study was to evaluate the OS of patients who received the combination of durvalumab plus cisplatin/gemcitabine compared to cisplatin/gemcitabine in two cohorts of patients treated outside of clinical trials.

Secondary endpoints of the study were PFS, objective response rate (ORR), and disease control rate (DCR) in the two cohorts of patients.

OS was defined as the time from the date of treatment initiation to the date of death; PFS was defined as the time from the date of treatment initiation to the date of disease progression or death or last follow-up whichever occurred first. ORR was assessed by the investigator and defined as the proportion of patients who achieved complete response (CR) or partial response (PR); disease control rate (DCR) was defined as the proportion of patients who achieved ORR or stable disease (SD). Treatment response was evaluated by computed tomography (CT) and categorized as CR, PR, SD or progressive disease (PD) by local review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Finally, an exploratory analysis on potential prognostic and predictive factors in the cohort of patients who received durvalumab in combination with cisplatin/gemcitabine was performed.

Survival curves were estimated using the product-limit method of Kaplan-Meier. The role of stratification factors was analyzed with log-rank tests.

Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model.

Categorical variables were compared using Fisher exact test.

A propensity score matching analysis was performed. A propensity score model was developed to control the results for baseline variable imbalances between the treatment ‘arms. A multivariate logistic regression analysis was applied to calculate the propensity score.

A p value <0.05 was considered statistically significant.

The predictive role of baseline characteristics was evaluated through the interaction test.

A MedCalc package (MedCalc® version 20.2) was used for statistical analysis.

3. RESULTS

3.1. Study Population

Overall, 358 patients were enrolled at 17 Italian sites and included in the analysis: 213 patients received cisplatin/gemcitabine alone, and 145 received durvalumab in combination to cisplatin/gemcitabine. The two cohorts of patients were quite homogeneous in terms of demographic and disease characteristics, except for the age, since in the cohort who received durvalumab in combination to cisplatin/gemcitabine there was a higher proportion of patients older than 70 years. Patient demographics and disease characteristics are reported in table 1. At data cutoff (December 1, 2022), the median duration of follow-up was 8.5 months (95% CI 4.2-10.9) for patients who received durvalumab in combination to cisplatin/gemcitabine compared to 30.1 months (95% CI 22.1-44.9) for patients who received cisplatin/gemcitabine alone.

3.2. Survival Analysis

Overall, 209 patients died during treatment: 82% in the cisplatin/gemcitabine arm, and 18% in the cisplatin/gemcitabine plus durvalumab arm. At the univariate analysis for OS, the addition of durvalumab to cisplatin/gemcitabine was found to have a prognostic impact, with median OS of 12.9 versus 11.2 months (HR 0.6, 95% CI 0.4-0.8, p=0.0016) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Figure 1A). In addition, CEA baseline normal levels versus > normal levels, CA 19-9 baseline normal levels versus > normal levels, neutrophil-lymphocyte ratio (NLR) ≤3 versus >3 and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 versus >0 resulted to have a positive prognostic impact at univariate analysis. After adjustment for unbalanced clinical covariates and for all the variables with a prognostic impact at the univariate analysis, the multivariate analysis for OS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (HR 0.5, 95% CI 0.3-0.8, p=0.0017) (Table 2).

At the univariate analysis for PFS, the addition of durvalumab to cisplatin/gemcitabine resulted to have a prognostic impact, with median PFS of 8.9 months compared to 6.0 months (HR 0.6, 95% CI 0.4-0.7, p≤0.0001) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Figure 1B). In addition, baseline CEA and CA 19-9 levels, NLR, and ECOG PS resulted to have a prognostic impact at univariate analysis. After adjustment for unbalanced clinical covariates and for all variables with a prognostic impact at the univariate analysis, the multivariate analysis for PFS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (HR 0.5, 95% CI 0.4-0.7, p=0.0017 f) (Table 3).

Subgroup analysis showed a survival benefit for all subgroups of patients, with patients >70 years and those with locally advanced disease having the best survival (Figure 2).

The interaction test highlighted NLR≤3 and ECOG PS=0 as positive predictive factors for OS on cisplatin/gemcitabine plus durvalumab.

The combination of cisplatin/gemcitabine plus durvalumab showed a tendence toward a higher ORR which did not reach the statistical significance (p=0.1235), whereas DCR was significantly higher for the combination of chemo-immunotherapy compared to cisplatin/gemcitabine alone (p<0.000001) (Supplementary table 1, Supplementary Figure 1).

3.3. Survival Analysis after Propensity score Matching

After propensity score matching, 134 patients resulted to be treated with cisplatin/gemcitabine, and 134 patients resulted to be treated with cisplatin/gemcitabine and durvalumab.

Baseline patient characteristics were well-balanced between the groups (Table 2-Supplementary Materials).

At the univariate analysis for OS, patients who received cisplatin/gemcitabine plus durvalumab showed to have better mOS compared to those who received cisplatin/gemcitabine alone (12.9 Vs 11.2 months, respectively, HR 0.5, 95% CI 0.4-0.8, p=0.0020) (Figure 2A-Supplementary Materials). In addition, CEA baseline levels, CA 19-9 baseline levels, NLR and ECOG PS resulted to have a prognostic impact at univariate analysis. After adjustment for the variables with a prognostic impact at the univariate analysis, the multivariate analysis for OS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (HR 0.5, 95% CI 0.3-0.7, p=0.0009) (Table 3-Supplementary).

At the univariate analysis for PFS, patients who received cisplatin/gemcitabine plus durvalumab showed to have better mPFS compared to those who received cisplatin/gemcitabine alone (8.9 Vs 6.0 months, respectively, HR 0.6, 95% CI 0.4-0.8, p=0.0006) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Figure 2B-Supplementary Materials). In addition, baseline NLR, and ECOG PS resulted to have a prognostic impact at univariate analysis. After adjustment for the variables with a prognostic impact at the univariate analysis, the multivariate analysis for PFS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (HR 0.5, 95% CI 0.4-0.7, p=0.0001) (Table 4-Supplementary Materials).

3.4. Exploratory analysis in the durvalumab cohort

An exploratory analysis of prognostic factors in the cohort of patients who received durvalumab was performed. At univariate analysis, disease stage (locally advanced Vs metastatic), NLR (≤3 versus >3), and ECOG PS (0 versus >0) were found to have an impact on OS. The multivariate analysis confirmed NLR>3 (HR 2.6, 95% CI 1.2-5.5, p=0.0162) and ECOG PS >0 (HR 2.7, 95% CI 1.3-5.7, p=0.0065) as negative prognostic factors for OS (Table 4). At the univariate analysis, NLR (≤3 versus >3), and ECOG PS (0 versus >0) resulted to have an impact on PFS. The multivariate analysis confirmed NLR>3 (HR 1.9, 95% CI 1.2-3.0, p=0.0100) and ECOG PS >0 (HR 2.0, 95% CI 1.2-3.2, p=0.0050) as negative prognostic factors for PFS (Table 5).

4. DISCUSSION

In the present analysis the positive survival impact of durvalumab in combination with cisplatin/gemcitabine compared to cisplatin/gemcitabine alone has been confirmed in a real-world cohort of patients with locally advanced or metastatic BTC who received a first-line treatment. Significantly, after the propensity score matching analysis, the results have been confirmed. The survival outcomes observed in the present analysis are consistent with those of the phase III TOPAZ-1 trial, thus reinforcing the benefit derived by the addition of immunotherapy to platinum-based chemotherapy (13). Moreover, survival results in the cisplatin/gemcitabine cohort are very similar to those reported in the ABC-02 study, thus suggesting that no significant underestimation of survival outcomes was done for the control group of patients. A similar consideration could be done for ORR and DCR: the results achieved in both our cohorts, durvalumab plus cisplatin/gemcitabine and cisplatin/gemcitabine alone, are comparable to those reported in the phase III trials. Although a direct comparison between the present retrospective analysis and the TOPAZ-1 and ABC-02 prospective randomized trials cannot be done, results confirm the survival benefit of combining immunotherapy to chemotherapy in this setting (13,16). Our research team recently published the first real-world experience of durvalumab in combination with cisplatin/gemcitabine (15). Differently from our previous work, the present one evaluated both patients receiving durvalumab and patients receiving chemotherapy alone and highlighted the survival benefit provided by immunotherapy compared to a cohort of patients who received the previous first-line standard of care represented by cisplatin/gemcitabine. Interestingly enough, our subgroup analysis showed that both patients with intra- (iCCA) and extra-hepatic cholangiocarcinoma (eCCA) have a significant benefit from the addition of durvalumab to chemotherapy. Moreover, we observed a particular benefit of durvalumab in older patients and in patients with locally advanced disease. The link between cancer, response to treatments and aging is complex and not yet completely understood. Immune response has been highlighted to decrease in elderly patients in the so-called immunosenescence process, thus leading to the increased risk of cancer onset. Starting from the immunosenescence concept, a lower benefit from immunotherapy in elderly patients has been

hypothesized. Nevertheless, available data are controversial. A number of previous papers reported good survival results in elderly patients who received immunotherapy in several cancer settings, including advanced hepatocellular carcinoma (17-20). Even more, Kugel and colleagues previously reported a high rate of response to ICI in elderly patients with melanoma. Moreover, they observed a higher population of regulatory T cells (Tregs) in older mouse models, which could be associated to an increased response to immunotherapy (21). Further investigations focused on the complex interplay between cancer and immune microenvironment are needed to define the impact of aging on immunotherapy-related survival outcomes. The second subgroup of patients who in our analysis showed to benefit more from the combined treatment are patients with locally advanced disease, in line with the findings of the TOPAZ-1 trial. Similar results have been achieved in other oncology settings, where immunotherapy has been shown to work better in earlier tumor stages compared to metastatic stages in both preclinical and clinical studies (22-29). In BTC this result deserves attention. The survival benefit observed in patients with locally advanced disease, together with the high ORR, paves the way for future research focused on potential neoadjuvant strategies or conversion treatments. To date the only published trial on the role of systemic therapy in the neoadjuvant setting for patients with resectable iCCA is the NEO-GAP, which demonstrated the feasibility and safety of the chemotherapy combination of gemcitabine, cisplatin and nab-paclitaxel prior to resection for iCCA (30). To date, no data about the role of immunotherapy for BTC in the neoadjuvant setting are available. The good survival results obtained in the present analysis in patients with locally advanced disease might suggest a potential benefit in reducing the risk of recurrence after surgery. Furthermore, the high response rate leads to the hypothesis that investigations on the role of this combination could be interesting in terms of conversion treatment in patients with unresectable disease. Future investigations are needed to explore the role of chemo-immunotherapy in the pre-operative setting. In the second part of our work, we performed an exploratory analysis of potential prognostic and predictive factors for response in patients who received durvalumab in combination with cisplatin/gemcitabine, since no clinical factors that could guide treatment choice have been validated in clinical practice. Our analysis highlighted NLR≤3 and ECOG PS=0 to be both positive prognostic factors and predictive factors for response to durvalumab and cisplatin/gemcitabine. NLR has previously been defined as a potential surrogate of the systemic inflammatory status, since it considers two populations of immune cells with antithetical functions: neutrophils involved in the proinflammatory and carcinogenic process and lymphocytes with mainly cytotoxic and anticancer functions (31-38). A high value of NLR could reflect an immune system characterized by a proinflammatory and carcinogenic status, thus possibly interfering with the response to the treatment with durvalumab combined to cisplatin/gemcitabine. Deeper insights into the biological pathways underlying the interaction between cancer, immune microenvironment, and immune checkpoint inhibition are crucial to verify this hypothesis.

Concerning the prognostic and predictive role of ECOG PS, few considerations could be done. In other oncology setting, ECOG PS has been demonstrated to be a prognostic factor in patients receiving

immunotherapy alone and immunotherapy combined with chemotherapy (39-41). A disrupted balance of immune response due to advanced disease and/or comorbidities could explain a scarce or reduced response to ICI. Further studies are needed to investigate this topic.

Several limitations could be ascribed to the present analysis. First of all, the retrospective nature of the work could not exclude possible selection biases, despite the adjustment in multivariate analysis and the propensity score matching analysis that cannot replace level I evidence derived from prospective randomized trial. Secondly, due to the multicenter nature of the study, the PFS data have to be contextualized and a slight difference in tumor assessment modalities and time-points between the institutes has to be considered. Moreover, an accurate comparison in terms of safety profile was not possible, due to the lack of data in the cohort of patients who received cisplatin and gemcitabine. Indeed, despite the high importance to make investigations in the real-world setting, some data could be missing thus making the analysis difficult and affected by bias. Finally, results of the TOPAZ-1 trial have been recently published, and durvalumab is available from January 2022, thus the median follow up of patients on durvalumab plus cisplatin/gemcitabine is significantly shorter compared to that of patients who received cisplatin/gemcitabine. Nevertheless, even considering the differences between prospective randomized trials and retrospective studies in the real-world setting, our results are consistent with those reported in the registration trials. Future updates after longer follow-up will be helpful to confirm the present results. Moreover, a comparative genomic analysis between patients who received cisplatin/gemcitabine alone compared to cisplatin/gemcitabine plus durvalumab would be of special interest with the aim to identify potential molecular prognostic and predictive biomarkers of response. Unfortunately, in past years molecular testing was not performed routinely, so only for a few patients who received cisplatin/gemcitabine alone the molecular profiling is available.

In conclusion, the present analysis adds a piece to our previously published data on the use of durvalumab in combination with cisplatin/gemcitabine in patients with advanced BTC, highlighting the survival benefit of adding immunotherapy to chemotherapy. Thus, the use of durvalumab in this setting was confirmed to provide a survival benefit, mainly in patients older than 70 years and with locally advanced disease.

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Figure Legends:

Figure 1. Kaplan Meier curves for OS and PFS.

Figure 2. Forest Plot analysis for OS

Suppl Figure 1. Response rate in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone.

Suppl Figure 2. Kaplan Meier curves for OS and PFS after propensity score matching

Tables