**Title:** Efficacy of Platinum Rechallenge in Metastatic Urothelial Carcinoma after Previous Platinum-Based Chemotherapy for Metastatic Disease

**Running Head:** Platinum Rechallenge in Metastatic Urothelial Ca

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**Abstract**

**Background:**

Fit patients with metastatic urothelial carcinoma (mUC) receive first-line platinum-based combination chemotherapy (fPBC) as standard of care, and may receive additional later-line chemotherapy after progression. Our study compares outcomes with subsequent platinum-based chemotherapy (sPBC) versus subsequent non-platinum-based chemotherapy (sNPBC).

**Materials and Methods:**

Patients from 28 international centers in the Retrospective International Study of Cancers of the Urothelium (RISC) who received fPBC for mUC and ≥2 cycles of subsequent chemotherapy were included in this study. A multivariable Cox proportional hazards model compared overall survival (OS) and progression-free survival (PFS).

**Results:**

135 patients received sPBC and 161 received sNPBC. Baseline characteristics were similar between groups, except patients who received sPBC had higher baseline hemoglobin, higher disease control rate with fPBC, and longer time since fPBC. OS was superior in the sPBC group (median 7.9 vs 5.5 months) in a model adjusting for comorbidity burden, performance status, liver metastases, number of fPBC cycles received, best response to fPBC, and time since fPBC (hazard ratio, 0.72; 95% CI, 0.53-0.98 [p=0.035]). There was no difference in PFS. More patients in the sPBC group achieved disease control than in the sNPBC group (57.4% vs 44.8%, p=0.041). Factors associated with achieving disease control in the sPBC group but not the sNPBC group included longer time since fPBC, achieving disease control with fPBC, and absence of liver metastases.

**Conclusion:**

After receiving fPBC for mUC, patients who received sPBC had better OS and disease control. This may help inform the choice of subsequent chemotherapy in patients with mUC.

**Implications for Practice:** Patients with progressive metastatic urothelial carcinoma after first-line platinum-based combination chemotherapy may now receive immuno-oncology agents, erdafitinib, or enfortumab vedotin; however, those ineligible for these later-line therapies or who progress after receiving them may be considered for subsequent chemotherapy. In this retrospective study of 296 patients, survival outcomes and disease control rates were better in those receiving subsequent platinum-based rechallenge compared to non-platinum-based chemotherapy, suggesting that patients should receive platinum rechallenge if clinically able. Disease control with platinum rechallenge was more likely with prior first-line platinum having achieved disease control, longer time since first-line platinum, and absence of liver metastases.

**Introduction**

The standard of care for fit patients with metastatic urothelial carcinoma (mUC) is first-line platinum-based combination chemotherapy (fPBC) with gemcitabine and cisplatin or the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Cisplatin-ineligible patients may receive gemcitabine and carboplatin or immune checkpoint inhibitors atezolizumab or pembrolizumab.1 Until recent years, options for subsequent therapies that improved survival after progression on a platinum-based therapy were limited, and generally consisted of further cytotoxic chemotherapy with either platinum-based or non-platinum-based regimens. Lacking evidence to inform the choice between rechallenging with platinum-based chemotherapy or switching to other cytotoxic chemotherapy agents associated with different mechanisms of action, providers often considered clinical features such as prior response to platinum and time from prior platinum chemotherapy to help guide the choice of subsequent regimen.2-4

Fortunately, since 2016, the United States Food and Drug Administration (FDA) has approved immune checkpoint inhibitors targeting PD-1 or PD-L1 for the post-platinum mUC setting, including the drugs avelumab, nivolumab, and pembrolizumab.5-7 Avelumab, used for maintenance therapy after fPBC for patients who have not progressed, has demonstrated an overall survival benefit over placebo.8 Patients with fibroblast growth factor receptor (FGFR) 2 or 3 alterations are now also eligible for erdafitinib as post-platinum therapy.9 Recently, enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, was approved in the post-platinum and post-anti-PD-1 or -PD-L1 setting.10 However, despite these vast improvements in the landscape of treatment for mUC, patients who are ineligible for these therapies or who subsequently progress may still be considered for further cytotoxic chemotherapy. Therefore, the question of optimal subsequent chemotherapy regimen after fPBC remains a clinically relevant one.

To help address this gap in knowledge, we examined differences in outcomes for patients treated with fPBC for mUC who later received subsequent platinum-based chemotherapy (sPBC) or subsequent non-platinum-based chemotherapy (sNPBC). We also sought to identify clinical factors that were associated with better outcomes with sPBC or sNPBC.

**Materials and Methods**

Data was abstracted from the Retrospective International Study of Cancers of the Urothelium (RISC), comprising 3,025 patients with muscle-invasive or advanced urothelial cancers treated at 28 international centers between 2005 and 2012. Patients were included for this analysis if they had mUC (either at diagnosis or after progression of localized disease), had received fPBC in the metastatic setting, and had received ≥2 cycles of later-line chemotherapy after fPBC. Patients who received prior platinum-based chemotherapy in the non-metastatic setting were excluded, as were patients with missing or incomplete data for treatment dates or survival status. Additional exclusion criteria are detailed in Figure 1. The primary endpoint of our study was overall survival (OS), with secondary endpoints including investigator-designated progression-free survival (PFS) and investigator-designated best response to subsequent chemotherapy. Disease control was defined as having an investigator-designated best response of stable disease, partial response, or complete response.

*Statistical Analyses*

Descriptive statistics, χ2, student’s *t*-test, and Mann-Whitney U-test were used to report and compare patient characteristics by sPBC versus sNPBC group. Kaplan-Meier curves for OS and PFS were performed, with time-to-event calculations starting from the first day of the first cycle of sPBC or sNPBC. A multivariable Cox proportional hazards model was used to adjust for Eastern Cooperative Oncology Group performance status (ECOG PS), Charlson Comorbidity Index (CCI), presence of liver metastases, number of fPBC cycles received, investigator-designated best response to fPBC, and time since completion of fPBC. Hemoglobin and albumin levels were excluded from the multivariable model due to a high proportion of missing values for these parameters. Analyses were performed using SAS (version 9.4, Cary NC). A two-sided p-value of ≤0.05 was considered statistically significant.

**Results**

From 2005 to 2012, a total of 3,025 patients were enrolled in the RISC database. After exclusion criteria were applied, 296 patients were eligible for analysis (Figure 1). 135 were treated with sPBC and 161 patients received sNPBC; the most common sNPBC regimens included taxanes (71.4%), gemcitabine (11.8%), or pemetrexed (5.0%).

Patient characteristics for the sPBC and sNPBC groups are compared in Table 1. The majority of baseline characteristics were similar between cohorts, including ECOG PS and comorbidity burden as assessed by the CCI. However, for the 251 patients for whom baseline hemoglobin at the start of fPBC was recorded, those who received sPBC tended to have higher baseline hemoglobin values (median 11.9 vs. 11.1 g/dL, p=0.004). Patients who received sPBC also tended to have better responses to fPBC compared to patients who received sNPBC (p=0.030) and to have experienced longer time between receipt of fPBC and initiation of subsequent chemotherapy (median 4.4 vs. 2.2 months, p=0.010).

OS curves for patients who received sPBC or sNPBC are displayed in Figure 2. OS was superior for patients receiving sPBC (median 7.9 months) compared to sNPBC (median 5.5 months) in a multivariable model adjusting for CCI, ECOG PS, presence of liver metastases, number of fPBC cycles received, best response to fPBC, and time since fPBC (HR 0.72, 95% CI 0.53-0.98, p=0.035) (Table 2). A similar analysis was performed for PFS (Figure 3, Table 2). In the multivariable model, there was no statistical difference in PFS for sPBC versus sNPBC (HR 0.83, 95% CI 0.64-1.08, p=0.159). Median PFS was 4.1 and 2.6 months for sPBC and sNPBC, respectively.

In terms of disease control rate with subsequent chemotherapy, 70 patients (57.4%) who received sPBC achieved disease control compared to 65 patients (44.8%) who received sNPBC (p=0.041). In the sPBC group, 33 patients (27.0%) achieved stable disease, 29 (23.8%) achieved partial response, and 8 (6.6%) achieved complete response; for sNPBC, 37 (25.5%), 21 (14.5%), and 7 (4.8%) patients achieved stable disease, partial response, and complete response, respectively.

A subgroup analysis was undertaken to compare factors associated with OS (data not shown) and PFS (Table 4) by type of subsequent chemotherapy. There were no unique associations with OS for either the sPBC or sNPBC group. However, for PFS, presence of liver metastases was associated with a higher likelihood of progression in the sPBC group (HR 1.78, 95% CI 1.14-2.79, p=0.011), as was having a best response to fPBC of stable disease as opposed to complete response (HR 2.75, 95% CI 1.32-5.72, p=0.007). For the sNPBC group, higher likelihood of progression was associated with having ECOG PS ≥2 compared to PS 0 (HR 2.03, 95% CI 1.28-3.22, p=0.003), CCI 1 compared to 0 (HR 2.22, 95% CI 1.19-4.14, p=0.013), and a higher number of fPBC cycles (HR 1.21, 95% CI 1.07-1.38, p=0.003).

Subgroup analysis was also performed for factors associated with achieving disease control with subsequent chemotherapy. Within the sPBC group, achieving disease control with fPBC was associated with a higher likelihood of achieving disease control with sPBC; 55 of 87 patients (63.2%) who achieved disease control with fPBC also achieved disease control with sPBC, while only 8 of the 27 patients (29.6%) who did not achieve disease control with fPBC achieved disease control with sPBC (p=0.002). The same association was not seen within the sNPBC group; 44 of 87 patients (50.5%) who achieved disease control with fPBC also achieved disease control with sNPBC, and 19 of 30 (38.8%) patients who did not achieve disease control with fPBC achieved disease control with SNPBC, a difference which did not reach statistical significance (p=0.185). Achieving disease control with fPBC was also associated with longer time since fPBC for patients who received sPBC (median 6.0 vs. 2.9 months, p=0.008) (Table 3), but not for patients who received sNPBC (median 2.2 vs. 2.6 months, p=0.769). Finally, in the sPBC group, liver metastases were negatively associated with the likelihood of achieving disease control with sPBC; only 14 of 32 patients (43.8%) with liver metastases achieved disease control with sPBC compared to 56 of 88 patients (63.6%) without liver metastases (p=0.038). Again, this association was not significant with patients who received sNPBC (36.2% vs. 49.0% respectively, p=0.147).

**Discussion**

In this retrospective study of 296 patients with mUC treated with further chemotherapy after having received fPBC for metastatic disease, OS and investigator-designated best response to subsequent chemotherapy was superior for patients who received sPBC compared to those who received sNPBC. These findings suggest that patients who are fit enough to receive additional platinum-based chemotherapy may indeed benefit more from platinum rechallenge than from receipt of non-platinum-based chemotherapy, particularly if disease response is clinically desirable due to symptom burden. That being said, median OS was on the order of several months in both groups, and even in the sPBC group, disease control rate was only 57.4%. Based on our subgroup analysis, achieving disease control with platinum rechallenge may be more likely in patients who achieved disease control with fPBC (as opposed to progressive disease) and who experienced a longer period of time between receipt of fPBC and initiation of subsequent chemotherapy, supporting clinical intuition that patients who achieve a deeper or more durable response to platinum-based chemotherapy in the first-line setting may also respond better to platinum rechallenge in later lines of therapy. Achieving disease control with sPBC was less likely if liver metastases were present, consistent with prior studies reporting visceral metastases as a risk factor associated with lower likelihood of response to platinum-based chemotherapy regimens.11-14 In contrast to the sPBC group, patients who received additional non-platinum-based chemotherapy had a higher likelihood of progression with greater ECOG PS and CCI, both indicators of the underlying “fitness” of the patient. In this group, progression was also more likely with a higher number of fPBC cycles received, which could possibly be explained by higher resistance to cytotoxic chemotherapy drugs or greater cumulative toxicity associated with prolonged prior chemotherapy administration.

To our knowledge, this study is unique in analyzing outcomes with platinum rechallenge in mUC after receipt of platinum-based combination chemotherapy for first-line treatment in the metastatic setting. Prior studies have examined the use of additional platinum chemotherapy after prior receipt of platinum-based chemotherapy in the non-metastatic setting, given perioperatively for localized disease to patients who ultimately developed advanced urothelial carcinoma, and largely showed that outcomes were better with additional platinum chemotherapy if ≥1 year had passed since receipt of prior platinum in the localized disease setting.15-17 These findings that longer time since prior platinum was associated with better outcomes after platinum rechallenge is concordant with our results. Not surprisingly, in our study, where fPBC was received by patients for metastatic and not localized disease, median time since prior platinum was much shorter and on the order of a few months.

This retrospective and non-randomized study has several limitations. First, baseline differences between patients almost certainly influenced whether clinicians recommended sPBC versus sNPBC, and so caution must be used when comparing the two groups. Although baseline hemoglobin values were slightly higher and patients appeared to have a higher initial disease control rate and time since fPBC in the sPBC group, performance status and comorbidity burden, as estimated by the CCI, were similar. We were unable to include hemoglobin and albumin levels in our multivariable model due to the number of missing values for these parameters in our data, and there may be other factors not accounted for in our model which may be relevant to clinicians and patients selecting their next treatment approach. Nevertheless, despite these confounders, our data does support giving additional platinum-based chemotherapy over non-platinum-based chemotherapy to patients and suggest that the superior activity of platinum agents in urothelial carcinoma supersedes potential concerns that re-exposing patients to platinum may result in decreased effect the second time around. Next, designations of disease response or progression were investigator-defined without formally mandated criteria such as RECIST 1.1 or standardized criteria for imaging frequency, affecting both recorded best response to therapy and date of progression; unfortunately, this reflects the variability in real-world practice patterns. This study data was collected prior to the advent of FDA-approved immuno-oncology agents, erdafitinib, and enfortumab vedotin for mUC; therefore, though we believe our findings are still helpful to clinicians choosing between sPBC and sNPBC for patients with mUC, patients in the modern era will differ from our study population in that they will have likely received some of these newer agents prior to consideration of subsequent chemotherapy. Finally, though the RISC database includes patients treated at 28 international sites over a number of years, our sample size does limit the power of our analyses, particularly in our multivariable model.

**Conclusion**

Patients with mUC who have progressed after treatment with platinum-based combination chemotherapy in the first-line setting now may receive immuno-oncology agents, erdafitinib, or enfortumab vedotin as later-line therapy; however, patients ineligible for these therapies or who progress after receiving them may still be considered for subsequent chemotherapy. In our study, patients who were rechallenged with platinum-based chemotherapy experienced longer survival and better disease response than those who received non-platinum-based chemotherapy, suggesting that patients should receive platinum rechallenge if clinically able. Achieving disease control with platinum rechallenge appears more likely when patients have achieved disease control with prior platinum, have experienced a longer time since prior platinum, and do not have liver metastases.

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**Figure Legends**

**Figure 1 – CONSORT Diagram**

CONSORT diagram demonstrating how patients from the Retrospective International Study of Cancers of the Urothelium (RISC) database were selected for analysis in our study.

**Figure 2 – Overall Survival Analysis**

Kaplan-Meier curves of overall survival (OS) by subsequent platinum-based chemotherapy (sPBC) versus subsequent non-platinum-based chemotherapy (sNPBC), with median survival times reported. OS was superior for patients receiving sPBC in a multivariable model adjusting for several baseline factors, as detailed in Table 2. HR indicates hazard ratio; CI, confidence interval.

**Figure 3 – Progression-Free Survival Analysis**

Kaplan-Meier curves of progression-free survival (PFS) by subsequent platinum-based chemotherapy (sPBC) versus subsequent non-platinum-based chemotherapy (sNPBC), with median survival times reported. There was no statistical difference in PFS in a multivariable model adjusting for several baseline factors, as detailed in Table 2. HR indicates hazard ratio; CI, confidence interval.

**Table 1 – Patient Characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **sPBC (n=135)a; N (%)** | **sNPBC (n=161)a; N (%)** | **P-value** |
| **Age in Years at Diagnosis; Median (IQR)** | 64 (57-70) | 65 (58-73) | 0.144 |
| **Female Gender** | 27 (20.1%) | 31 (19.2%) | 0.847 |
| **Former/Current Smoker** | 80 (69.6%) | 110 (74.3%) | 0.129 |
| **Charlson Comorbidity Index (CCI)** |  |  | 0.292 |
| 0 | 60 (44.4%) | 70 (43.5%) |  |
| 1 | 14 (10.4%) | 9 (5.6%) |  |
| 2 | 23 (17.0%) | 38 (23.6%) |  |
| ≥3 | 38 (28.1%) | 44 (27.3%) |  |
| **ECOG Performance Status (ECOG PS)** |  |  | 0.141 |
| 0 | 31 (29.8%) | 25 (19.5%) |  |
| 1 | 57 (54.8%) | 73 (57.0%) |  |
| ≥2 | 16 (15.4%) | 30 (23.5%) |  |
| **Metastatic Disease at Diagnosis**  | 80 (59.3%) | 95 (59.0%) | 0.965 |
| **Brain Metastasesb** | 1 (0.8%) | 5 (3.1%) | 0.065 |
| **Liver Metastasesb** | 34 (26.2%) | 50 (31.3%) | 0.110 |
| **Hemoglobin, g/dL; Median (IQR)c** | 11.9 (10.7-13.1) | 11.1 (10.1-12.5) | 0.004 |
| **Albumin, g/dL; Median (IQR)c** | 3.8 (3.4-4.1) | 3.6 (3.3-3.9) | 0.431 |
| **Creatinine, mg/dL; Median (IQR)c** | 1.2 (1.0-1.5) | 1.2 (0.9-1.5) | 0.448 |
| **Number of fPBC Cycles Received** |  |  | 0.621 |
| 2 | 13 (9.6%) | 14 (8.7%) |  |
| 3-4 | 42 (31.1%) | 47 (29.2%) |  |
| 5-6 | 68 (50.4%) | 76 (47.2%) |  |
| ≥7 | 12 (8.9%) | 24 (14.9%) |  |
| **Best Response to fPBC**  |  |  | 0.030 |
| Complete Response | 16 (12.7%) | 7 (4.7%) |  |
| Partial Response | 50 (39.7%) | 47 (31.3%) |  |
| Stable Disease | 29 (23.0%) | 41 (27.3%) |  |
| Progressive Disease | 31 (24.6%) | 55 (36.7%) |  |
| **Received Non-Chemotherapy Treatment between fPBC and sPBC/sNPBCd** | 6 (4.4%) | 6 (3.7%) | 0.755 |
| **Months Elapsed since fPBC; Median (IQR)** | 4.4 (1.2-7.9) | 2.2 (0.9-5.6) | 0.010e |

Abbreviations: sPBC, subsequent platinum-based chemotherapy; sNPBC, subsequent non-platinum-based chemotherapy; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; fPBC, first-line platinum-based chemotherapy.

aTotal number of patients for some variables may be less than “n” due to missing values.
bPresence of brain or liver metastases assessed at time of diagnosis with metastatic disease.
cHemoglobin, albumin, and creatinine lab values assessed at time of initiation of fPBC.
dTreatment in between fPBC and sPBC/sNPBC included the drugs sunitinib, pazopanib, erlotinib, and cetuximab
eMann-Whitney U test used to compare nonparametric data.

**Table 2 – Factors Associated with Overall and Progression-Free Survival, Multivariable Model**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Risk of Death** | **Risk of Progression** |
| **HR (95% CI)** | **Standard Error** | **χ2** | **HR (95% CI)** | **Standard Error** | **χ2** |
| **sPBC vs. sNPBC** | 0.72 (0.53-0.98) | 0.16 | 0.035 | 0.83 (0.64-1.08) | 0.13 | 0.159 |
|  |  |  |  |  |  |  |
| **ECOG PS** |  |  |  |  |  |  |
| 1 vs. 0 | 1.52 (0.99-2.33) | 0.22 | 0.055 | 0.99 (0.73-1.34) | 0.16 | 0.931 |
| ≥2 vs. 0 | 2.02 (1.21-3.37) | 0.26 | 0.007 | 1.57 (1.01-2.44) | 0.23 | 0.048 |
| Unknown vs. 0 | 1.87 (1.16-2.96) | 0.24 | 0.010 | 1.15 (0.81-1.64) | 0.18 | 0.423 |
|  |  |  |  |  |  |  |
| **CCI** |  |  |  |  |  |  |
| 1 vs. 0 | 1.04 (0.59-1.83) | 0.29 | 0.904 | 1.31 (0.86-1.99) | 0.22 | 0.216 |
| 2 vs. 0 | 0.79 (0.52-1.19) | 0.21 | 0.259 | 0.87 (0.61-1.25) | 0.18 | 0.458 |
| ≥3 vs. 0 | 1.16 (0.80-1.67) | 0.19 | 0.437 | 1.11 (0.81-1.53) | 0.16 | 0.511 |
|  |  |  |  |  |  |  |
| **Liver Metastases**  |  |  |  |  |  |  |
| Yes vs. No | 1.39 (1.00-1.93) | 0.17 | 0.053 | 1.19 (0.90-1.59) | 0.15 | 0.229 |
| Unknown vs. No | 1.45 (0.57-3.70) | 0.48 | 0.434 | 0.56 (0.16-2.03) | 0.66 | 0.378 |
|  |  |  |  |  |  |  |
| **Number of fPBC cycles** | 1.07 (0.96-1.19) | 0.06 | 0.217 | 1.15 (1.04-1.27) | 0.05 | 0.007 |
|  |  |  |  |  |  |  |
| **Best Response to fPBC**  |  |  |  |  |  |  |
| PR vs. CR | 0.83 (0.45-1.19) | 0.32 | 0.565 | 1.21 (0.73-1.99) | 0.26 | 0.467 |
| SD vs. CR | 0.92 (0.48-1.55) | 0.33 | 0.806 | 1.47 (0.87-2.49) | 0.27 | 0.149 |
| PD vs. CR | 1.02 (0.52-1.77) | 0.34 | 0.946 | 1.76 (0.98-3.19) | 0.30 | 0.060 |
| Unknown vs. CR | 0.84 (0.37-2.00) | 0.41 | 0.676 | 1.64 (0.90-3.01) | 0.31 | 0.108 |
|  |  |  |  |  |  |  |
| **Months Elapsed since fPBC** | 0.99 (0.96-1.01) | 0.01 | 0.270 | 0.98 (0.97-1.00) | 0.01 | 0.082 |

Abbreviations: HR, hazard ratio; CI, confidence interval; sPBC, subsequent platinum-based chemotherapy; sNPBC, subsequent non-platinum-based chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CCI, Charlson Comorbidity Index; fPBC, first-line platinum-based chemotherapy; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

**Table 3 – Factors Associated with Achieving Disease Control with Subsequent Chemotherapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Disease Control with Subsequent Chemotherapy(All Patients)** | **Disease Control with sPBC** | **Disease Control with sNPBC** |
| **Yes (n=135)a N (%)** | **No (n=132)a****N (%)** | **P-value** | **Yes (n=70)aN(%)** | **No (n=52)aN (%)** | **P-value** | **Yes (n=65)aN (%)** | **No (n=80)aN (%)** | **P-value** |
| **ECOG PS** |  |  | 0.065 |  |  | 0.384 |  |  | 0.334 |
| 0 | 32 (29.4%) | 20 (19.2%) |  | 19 (32.8%) | 10 (24.4%) |  | 13 (25.5%) | 10 (15.9%) |  |
| 1 | 63 (57.8%) | 57 (54.8%) |  | 33 (56.9%) | 22 (53.7%) |  | 30 (58.8%) | 35 (55.6%) |  |
| ≥2 | 14 (12.8%) | 27 (26.0%) |  | 6 (10.3%) | 9 (22.0%) |  | 8 (15.7%) | 18 (28.6%) |  |
| **CCI** |  |  | 0.345 |  |  | 0.403 |  |  | 0.910 |
| 0 | 60 (44.4%) | 61 (46.2%) |  | 32 (45.7%) | 25 (48.1%) |  | 28 (43.1%) | 36 (45.0%) |  |
| 1 | 14 (10.4%) | 6 (4.5%) |  | 10 (14.3%) | 3 (5.8%) |  | 4 (6.2%) | 3 (3.8%) |  |
| 2 | 26 (19.3%) | 27 (20.5%) |  | 11 (15.7%) | 7 (13.5%) |  | 15 (23.1%) | 20 (25.0%) |  |
| ≥3 | 35 (25.9%) | 38 (28.8%) |  | 17 (24.3%) | 17 (32.7%) |  | 18 (27.7%) | 21 (26.3%) |  |
| **Liver Metastases**  |  |  | 0.016 |  |  | 0.038 |  |  | 0.147 |
| Yes | 31 (23.0%) | 48 (36.9%) |  | 14 (20.0%) | 18 (36.0%) |  | 17 (26.2%) | 30 (37.5%) |  |
| No | 104 (77.0%) | 82 (63.1%) |  | 56 (80.0%) | 32 (64.0%) |  | 48 (73.9%) | 50 (62.5%) |  |
| **Number of fPBC cycles** |  |  | 0.340 |  |  | 0.193 |  |  | 0.703 |
| 2 | 14 (10.4%) | 11 (8.3%) |  | 7 (10.0%) | 5 (9.6%) |  | 7 (10.8%) | 6 (7.5%) |  |
| 3-4 | 43 (31.9%) | 31 (23.5%) |  | 24 (34.3%) | 11 (21.1%) |  | 19 (29.2%) | 20 (25.0%) |  |
| 5-6 | 63 (46.7%) | 70 (53.0%) |  | 35 (50.0%) | 28 (53.8%) |  | 28 (43.1%) | 42 (52.5% |  |
| ≥7 | 15 (11.1%) | 20 (15.2%) |  | 4 (5.7%) | 8 (15.4%) |  | 11 (16.9%) | 12 (15.0%) |  |
| **Best Response with fPBC**  |  |  | 0.002 |  |  | 0.002 |  |  | 0.185 |
| Disease Control | 99 (78.6%) | 75 (60.5%) |  | 55 (87.3%) | 32 (62.7%) |  | 44 (69.8%) | 43 (58.9%) |  |
| Progressive Disease | 27 (21.4%) | 49 (39.5%) |  | 8 (12.7%) | 19 (37.3%) |  | 19 (30.2%) | 30 (41.1%) |  |
| **Months Elapsed since fPBC; Median (IQR)** | 3.9 (1.0-8.9) | 2.8 (1.1-5.5) | 0.051b | 6.0 (1.5-10.1) | 2.9 (1.1-5.4) | 0.008b | 2.2 (0.9-6.6) | 2.6 (1.0-5.6) | 0.769b |

Abbreviations: sPBC, subsequent platinum-based chemotherapy; sNPBC, subsequent non-platinum-based chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CCI, Charlson Comorbidity Index; fPBC, first-line platinum-based chemotherapy; IQR, interquartile range.

aTotal number of patients for some variables may be less than “n” due to missing values. Due to rounding, some columns may not add up to 100.0%.
bMann-Whitney U test used to compare nonparametric data.

**Table 4 – Factors Associated with Progression-Free Survival, Subgroup Analysis by Type of Subsequent Chemotherapy**

|  |  |  |
| --- | --- | --- |
| **Variable** | **sPBC, Risk of Progression** | **sNPBC, Risk of Progression** |
| **HR (95% CI)** | **Standard Error** | **χ2** | **HR (95% CI)** | **Standard Error** | **χ2** |
| **ECOG PS** |  |  |  |  |  |  |
| 1 vs. 0 | 0.97 (0.61-1.52) | 0.23 | 0.883 | 1.01 (0.67-1.51) | 0.20 | 0.970 |
| ≥2 vs. 0 | 1.18 (0.53-2.65) | 0.41 | 0.683 | 2.03 (1.28-3.22) | 0.24 | 0.003 |
| Unknown vs. 0 | 1.19 (0.69-2.06) | 0.28 | 0.530 | 1.06 (0.66-1.72) | 0.25 | 0.802 |
|  |  |  |  |  |  |  |
| **CCI** |  |  |  |  |  |  |
| 1 vs. 0 | 0.98 (0.52-1.83) | 0.32 | 0.937 | 2.22 (1.19-4.14) | 0.32 | 0.013 |
| 2 vs. 0 | 0.98 (0.52-1.82) | 0.32 | 0.942 | 0.84 (0.53-1.33) | 0.23 | 0.464 |
| ≥3 vs. 0 | 1.01 (0.67-1.53) | 0.21 | 0.947 | 1.39 (0.88-2.17) | 0.23 | 0.155 |
|  |  |  |  |  |  |  |
| **Liver Metastases**  |  |  |  |  |  |  |
| Yes vs. No | 1.78 (1.14-2.79) | 0.23 | 0.011 | 0.97 (0.68-1.39) | 0.18 | 0.859 |
| Unknown vs. No | 0.35 (0.07-1.84) | 0.85 | 0.214 | 1.07 (0.57-1.99) | 0.32 | 0.839 |
|  |  |  |  |  |  |  |
| **Number of fPBC cycles** | 1.10 (0.94-1.29) | 0.08 | 0.248 | 1.21 (1.07-1.38) | 0.07 | 0.003 |
|  |  |  |  |  |  |  |
| **Best Response to fPBC**  |  |  |  |  |  |  |
| PR vs. CR | 1.42 (0.72-2.81) | 0.35 | 0.313 | 0.82 (0.41-1.66) | 0.36 | 0.580 |
| SD vs. CR | 2.75 (1.32-5.72) | 0.37 | 0.007 | 0.88 (0.42-1.86) | 0.38 | 0.738 |
| PD vs. CR | 2.15 (0.95-4.87) | 0.42 | 0.066 | 1.49 (0.68-3.27) | 0.40 | 0.320 |
| Unknown vs. CR | 1.17 (0.46-3.00) | 0.48 | 0.747 | 1.76 (0.75-4.09) | 0.43 | 0.193 |
|  |  |  |  |  |  |  |
| **Months Elapsed since fPBC** | 0.98 (0.94-1.02) | 0.02 | 0.295 | 0.99 (0.97-1.01) | 0.01 | 0.381 |

Abbreviations: HR, hazard ratio; CI, confidence interval; sPBC, subsequent platinum-based chemotherapy; sNPBC, subsequent non-platinum-based chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CCI, Charlson Comorbidity Index; fPBC, first-line platinum-based chemotherapy; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.