Multicenter Evaluation of Neoadjuvant and Induction Gemcitabine-Carboplatin versus Gemcitabine-Cisplatin Followed by Radical Cystectomy for Muscle-Invasive Bladder Cancer

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Abstract

Purpose

Cisplatin-based chemotherapy followed by radical cystectomy (RC) is recommended in patients with muscle-invasive bladder cancer (MIBC). However, up to 50% of patients are cisplatin-ineligible. The aim of this study was to compare clinical outcomes after ≥3 cycles of preoperative gemcitabine-carboplatin (gem-carbo) versus gemcitabine-cisplatin (gem-cis).

Methods

We identified 1865 patients treated at 19 centers between 2000 and 2013. Patients were included if they had received ≥3 cycles of neoadjuvant (cT2-4aN0M0) or induction (cTanyN+M0) gem-carbo or gem-cis followed by RC.

Results

We included 747 patients treated with gem-carbo (n=147) or gem-cis (n=600). Patients treated with gem-carbo had a higher Charlson Comorbidity Index (p=0.016) and more clinically node-positive disease (32% versus 20%; p=0.013). The complete pathological response (pCR; ypT0N0) rate did not significantly differ between gem-carbo and gem-cis (20.7% versus 22.1%; p=0.73). Chemotherapeutic regimen was not significantly associated with pCR (OR: 0.99 [95%CI, 0.61-1.59]; p=0.96), overall survival (OS) (HR: 1.20 [95%CI, 0.85-1.67]; p=0.31), or cancer-specific survival (CSS) (HR: 1.35 [95%CI, 0.93-1.96]; p=0.11). Median OS of patients treated with gem-carbo and gem-cis was 28.6 months (95%CI 18.1-39.1) and 45.1 months (95%CI 32.7-57.6)(p=0.18), respectively. Median CSS of patients treated with gem-carbo and gem-cis was 28.8 months (95%CI 9.8-47.8) and 71.0 months (95%CI median not reached)(p=0.02), respectively. Subanalyses of the neoadjuvant and induction setting did not show significant survival differences.

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97 **Conclusion**

98 Our results show that a subset of cisplatin-ineligible patients with MIBC achieve pCR on gem-carbo and
99 that survival outcomes seem comparable to gem-cis provided patients are able to receive ≥3 cycles and
100 undergo RC.

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Introduction

Cisplatin-based chemotherapy prior to radical cystectomy (RC) is recommended in patients with muscle-invasive bladder cancer (MIBC)[1]. Neoadjuvant chemotherapy aims to eliminate (micro-)metastases and leads to an absolute overall survival benefit of 5-8% at five years[2,3]. However, up to 50% of MIBC patients are considered unfit for cisplatin, mainly due to poor renal function, poor performance status or other comorbidities[4].

Most MIBC patients who are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. Although carboplatin-containing chemotherapy has not been proven equivalent to cisplatin regimens, the combination of carboplatin and gemcitabine (gem-carbo) is considered standard of care for cisplatin-ineligible patients with metastatic or locally advanced, unresectable urothelial cancer[1]. In the neoadjuvant setting, however, guidelines do not recommend the use of gem-carbo due to lack of evidence in the preoperative setting and because of its perceived inferior efficacy in the metastatic setting compared to cisplatin-based chemotherapy, which is largely driven by a small RCT[5] and indirect comparison of trials and retrospective studies[6,7].

Remarkably, more recent data from the phase-3 DANUBE-trial suggest similar survival of patients treated with gem-carbo and gem-cis[8]. Although that study focused on metastatic bladder cancer, patients with unresectable, locally advanced disease and regional lymph-node metastases were also included. These data warrant re-exploration of gem-carbo for cisplatin-ineligible patients in the preoperative (neoadjuvant or induction) setting as well. Moreover, in a recent Dutch nationwide cohort study, no significant survival benefit was observed for gem-cis over gem-carbo for first-line chemotherapy in metastatic bladder cancer[9]. Therefore, the aim of the present study was to compare pathological response and survival after at least three cycles of neoadjuvant or induction gem-carbo versus gem-cis followed by RC for MIBC, in a multicenter evaluation.

Materials and Methods

Study population

Approval of the institutional review board was obtained and data sharing agreements were exchanged between the 19 different hospitals in Europe and North America between 2000–2013. We performed a retrospective analysis of a large multi-institutional series of 1865 patients treated with neoadjuvant (cT2-4aN0M0) or induction (cT4bN0M0 or cTanyN+M0) chemotherapy followed by RC for MIBC. We have previously reported results from this database[10,11]. This present analysis was based on an extended database and maintained different inclusion and exclusion criteria. Patients were included if they had received at least three cycles of either gem-cis or gem-carbo. Moreover, the current study included patients without (cT2-4bN0M0) and with (cTanyN+M0) lymph node metastases. Patients treated with other regimens (e.g. methotrexate-vinblastine-doxorubine-cisplatin, taxanes, single-agent regimens) were excluded. Only patients with urothelial carcinoma were included (glandular and squamous differentiation allowed). Patients with non-muscle invasive (cT1/is/aN0) or metastatic (cM1) disease as well as those with inconclusive staging (cTx/Nx/Mx) were excluded. Patients who did not complete at least three cycles or switched chemotherapy regimen were also excluded. The full details of pre-operative assessment and surgical details are included in the **Supplementary Methods**.

Endpoints

Endpoints of this study include pathological response, assessed by histopathological evaluation of the RC specimen, according to the 2010 American Joint Committee on Cancer classification. Complete pathological response (pCR) was defined as ypT0N0 and partial pathological response (pPR) as downstaging to non-muscle invasive bladder cancer without lymph node involvement (≤ypT1N0). Non-

response was defined as residual muscle-invasive disease (≥ypT2N0) and/or lymph node metastases (ypTanyN+).

Statistical Analysis

The Mann-Whitney U test was used to compare means of non-normally distributed continuous data. Categorical variables were compared with Chi-square tests and Bonferroni adjusted post hoc tests. Multivariable logistic regression analysis for prediction of pCR and pPR included patient characteristics (age, gender, Charlson Comorbidity Index (CCI) and Eastern Cooperative Oncology Group (ECOG) performance status), chemotherapy regimen, and clinical tumor and nodal stage.

Secondly, we compared overall survival (OS) and cancer-specific survival (CSS), defined as the time interval between the start of neoadjuvant or induction chemotherapy to time of death from any cause or from MIBC, respectively. OS and CSS were analyzed using the Kaplan Meier method and compared with the log-rank test. Patients alive at the end of follow-up were censored at that date. Cox proportional hazards regression models were used to identify independent predictors of survival and calculate hazard ratios (HRs). Variables for multivariable Cox proportional hazards regression analysis included patient characteristics (age, comorbidities), chemotherapy regimen, and tumor characteristics (clinical tumor and nodal stage). All reported p-values are two-sided with statistical significance considered at ≤0.05. Analyses were performed using SPSS v23 software (IBM SPSS statistics; IBM Corp, Amonk, NY, USA).

Results

Supplementary Figure 1 depicts the selection of patients for analysis. Of 1865 patients in total, 747 patients met the inclusion criteria, of whom 600 (80.3%) received gem-cis and 147 (19.7%) gem-carbo. Stratified by setting, 579 of 747 patients in our cohort (77.5%) were treated in the neoadjuvant setting (gem-cis, n=479 (83%); gem-carbo, n=100 (17%)) and 168 of 747 (22.5%) were treated in the induction setting (gem-cis, n=121 (72%); gem-carbo, n=47 (28%)).

Baseline patient and tumor characteristics are summarized in **Table 1**. Patients treated with gem-carbo were significantly older than those treated with gem-cis and both CCI and ECOG performance status were higher in patients treated with gem-carbo. Furthermore, patients treated with gem-carbo were more likely to have hydronephrosis and a cT4 tumor compared to patients treated with gem-cis. In addition, more patients treated with gem-carbo had clinically node-positive disease, meaning that these patients were more likely treated in the induction setting than patients treated with gem-cis.

Regarding pathological response, pCR rates did not statistically differ between patients receiving gem-carbo vs gem-cis (20.7% vs 22.1%, respectively (p=0.727). The pPR rate was 32% for gem-carbo and 43% for gem-cis (p=0.019). In multivariable analysis **(Table 2)**, lower cT-stage was the only factor associated with higher pCR rates (OR 0.64, 95%CI 0.44-0.93; p=0.019). Both lower cT-stage (OR 0.57, 95%CI 0.41-0.78; p<0.001) and lower age (OR 0.98, 95%CI 0.97-0.99; p=0.035) were significant factors associated with higher pPR rates. Type of chemotherapy regimen was not associated with pCR (OR 0.99, 95%CI 0.61-1.59) or pPR (OR 0.77, 95%CI 0.51-1.17).

Median follow-up of the entire cohort was 14.3 months. Median follow-up of the survivors was 17.9 months. Median OS was 28.6 months (95%CI, 18.1-39.1) for patients treated with gem-carbo and 45.1 months (95%CI, 32.7-57.6) for those treated with gem-cis (p=0.18). Median CSS was 28.8 months for

patients treated with gem-carbo (95%CI, 9.8-47.8) and 71.0 months (95%CI, median survival not reached) for gem-cis (p=0.02). **Figure 1** shows the Kaplan Meier curves for CSS and OS in these patients.

In Cox proportional hazards regression analyses, type of chemotherapy was not a significant factor associated with OS (HR: 1.20 [95%CI, 0.85-1.67]; p=0.31) or CSS (HR: 1.35 [95%CI, 0.93-1.96]; p=0.113) **(Table 2)**. Separate analyses of patients in the neoadjuvant setting and the induction setting showed that neither OS nor CSS were significantly different between patients treated with gem-cis and gem-carbo (**Suppl. Fig2-3**). Instead, high cT-stage was a predictive factor for reaching pCR (OR: 0.64 [95%CI, 0.44-0.93]; p=0.019) and pCD (OR: 0.57 [95%CI, 0.41-0.78]; p<0.001). Furthermore, high CCI was associated with OS (HR: 0.029 [95%CI, 1.05-2.69]; p=0.029) and CSS (HR: 1.65 [95%CI, 0.995-2.74]; p=0.003). Finally, high cT-stage was associated with OS (HR: 1.44 [95%CI, 1.07-1.94]; p=0.017) and CSS (HR: 1.55 [95%CI, 1.11-2.15]; p=0.009).

Discussion

The present multicenter study was carried out to evaluate clinical outcomes after neoadjuvant or induction gem-carbo versus gem-cis, followed by RC for MIBC. This was done to explore gem-carbo as an alternative preoperative regimen for patients with MIBC who are ineligible for cisplatin, which is an important subset comprising up to 50% of patients(4). Focusing on patients who completed a minimum of three cycles and underwent RC, we found comparable complete response rates among both treatment groups. However, non-response (i.e. ≥ypT2N0 or ypTanyN+) was more common in patients treated with gem-carbo. This may be attributed to the fact that cisplatin-ineligibility is the result of various comorbidities. Hence, patients treated with gem-carbo had poorer performance status and more clinical nodal involvement than patients treated with gem-cis. Despite poor performance status, patients treated with gem-carbo were as likely to complete ≥3 treatment cycles as patients treated with gem-cis. Moreover, in multivariable analysis, the aforementioned patient and tumor characteristics, rather than type of chemotherapy regimen, were found to be factors associated with pathological response rates.

A second key finding of our study was that there was no significant difference of median OS or in the Kaplan Meier analysis of OS between the gem-cis and the gem-carbo group. In contrast, median CSS was significantly longer for patients treated with gem-cis and the time-to-event analysis was in favor of gem-cis. However, chemotherapeutic regimen did not remain a significant predictor of CSS in multivariable regression analysis. Most likely, higher disease stage (induction setting (≥cTanyN1-3M0)) in combination with significant residual disease may explain shorter CSS for patients treated with gem-carbo, as these variables were the only significant ones associated with survival in multivariable analysis. Importantly, further subanalyses of the neoadjuvant and induction settings separately showed no significant difference in CSS or OS between patients treated with gem-carbo and gem-cis. This underlines the prognostic impact of disease stage over the type of chemotherapy regimen in this series.

To the best of our knowledge, this is the first and largest multicenter study directly comparing the clinical efficacy of gem-carbo vs gem-cis in the neoadjuvant and induction setting. So far, there are limited reports showing conflicting results. A number of small, mostly single institution retrospective series suggested that preoperative carboplatin-based chemotherapy for MIBC leads to pCR rates comparable to cisplatin-based regimens[12,13]. Contrarily, others showed that gem-carbo is less effective[14]. In our own prior analysis, we observed the best outcomes in patients treated with cisplatin-based regimens[10,11]. However, in that study we did not differentiate between gem-carbo and other, possibly less effective non-cisplatin-based regimens, and we included methotrexate-vinblastine-doxorubicin-cisplatin. To overcome these limitations, we decided to focus strictly on gem-carbo vs gem-cis and assess efficacy after at least three cycles.

Our results showed that 21% and 32% of patients treated with gem-carbo achieved pCR and pPR, respectively. This is consistent with pathological response rates reported in other studies on neoadjuvant/induction gem-carbo (16.3%-31%)[11,12,15,16]. In contrast, the pCR rate for gem-cis was lower in this cohort than previously reported in clinical trials (22% versus 28%-38%)[17]. A possible explanation for this difference may include the fact that we also included patients treated in the induction setting while clinical trials were only conducted in the neoadjuvant setting and that clinical trials often yield more favorable results than 'real-world' cohorts.

The rationale to perform the present analysis was provided by recent findings of the phase-3 DANUBE trial[8]. In this study, Powles et al. investigated survival of 1032 patients who received standard of care platinum-based chemotherapy (gem-cis or gem-carbo) versus durvalumab (a PD-L1 inhibitor) vs durvalumab with tremelimumab (a CTLA-4 inhibitor), as first-line treatment for locally advanced, unresectable or metastatic urothelial carcinoma. In the chemotherapy arm of this trial, both regimens appeared to have similar efficacy outcomes in the cisplatin-eligible and cisplatin-ineligible populations[8]. This contrasts the generally perceived superiority of cisplatin over carboplatin as first-line therapy for

metastatic disease, the evidence for which is summarized in a meta-analysis of 4 randomized studies in metastatic urothelial carcinoma[18]. However, a recent re-analysis of this meta-analysis did not observe significant survival benefit of cisplatin over carboplatin when an alternative censoring scenario for survival analysis is maintained[19]. Finally, a meta-analysis of first-line treatment of cisplatin-ineligible patients showed that first-line immune checkpoint inhibition was not more effective than gem-carbo[20]. These findings in the metastatic setting warranted re-exploration of the efficacy of gem-carbo.

Alternatively, cisplatin-ineligible patients in the preoperative setting could also be treated with upfront RC. The available evidence of gem-carbo in the preoperative setting is limited and of low quality. However, two retrospective studies (n=150-171 patients) comparing gem-carbo to upfront RC show that both CSS and OS were significantly in favor of treatment with preoperative gem-carbo[13,16]. Although the evidence on systemic preoperative treatment for cisplatin-ineligible patients is limited, gem-carbo seems preferable relative to other alternatives, which is further supported by our results. However, more prospective data is required to make recommendation for gem-carbo in the neoadjuvant setting.

There are limitations to the study, including its retrospective design and lack of randomization. Furthermore, although our dataset is the largest to address preoperative gem-carbo, a larger sample size might be required to demonstrate equivalence or non-inferiority. Moreover, only patients who completed at least three cycles and underwent subsequent surgery were included in the present analysis, and we did not correct for number of cycles received. An intention-to-treat analysis, in which all patients were analyzed who started gem-cis or gem-carbo in the neoadjuvant or induction setting, may have resulted in lower pathological response rates. This could have affected the gem-carbo group disproportionately since more patients in this group were treated in the induction setting, where patients are more likely not to undergo RC if they have an inadequate clinical response to upfront chemotherapy. In addition, median follow-up time for these cohorts were relatively short. Finally, patients with gem-cis can transition to gem-carbo if needed, but patients starting gem-carbo do not typically have a second option if they do not

tolerate the selected chemotherapy regimen. We aimed to control for this by including only patients with a minimum of 3 cycles of one regimen without cross-over.

In conclusion, this multicenter analysis shows that a subset of cisplatin-ineligible patients with MIBC achieve pathological response to gem-carbo at RC, and that survival outcomes were comparable to gem-cis in the neoadjuvant and induction settings, if patients are able to receive at least 3 cycles and undergo RC. These results add to the evidence that the efficacy and role of gem-carbo for cisplatin-ineligible patients in the preoperative setting, for whom systemic treatment options are limited, should be re-evaluated.

Competing interests

No funding was received for conducting this study. The authors have no relevant financial or non-financial interests to disclose.

Author contribution

Sarah Einerhand, Bas van Rhijn, Peter Black and Laura Mertens contributed to study conception and design. Data collection was performed by Homayoun Zargar, Adrian Fairey, Colin Dinney, Maria Mir, Laura-Maria Krabbe, Michael Cookson, Niels-Erik Jacobson, Jeffrey Montgomery, Nikhil Vasdev, Evan Yu, Evanguelos Xylinas, Wassim Kassouf, Marc Dall'Era, Srikala Sridhar, Jonathan McGrath, Jonathan Aning, Shahrokh Shariat, Jonathan Wright, Andrew Thorpe, Todd Morgan, Jeff Holzbeierlein, Trinity Bivalacqua, Scott North, Daniel Barocas, Yair Lotan, Petros Grivas, Jorge Garcia, Andrew Stephenson, Jay Shah, Siamak Daneshmand, Philippe Spiess, Laura Mertens. Data analysis was performed by Anna Black. The first draft of the manuscript was written by Sarah Einerhand, Bas van Rhijn, Peter Black and Laura Mertens and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics statement

This study has been approved by the Institutional Review Board of the Netherlands Cancer Institute (IRBd18126). The present study was conducted in accordance with Good Clinical Practice guidelines and with provisions of the Declaration of Helsinki.

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