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Original Article

Comparative Efficacy and Toxicity of Gemcitabine–Cisplatin vs. Gemcitabine–Carboplatin in Metastatic Carcinoma of the Urinary Bladder: A Retrospective Review

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Abstract

Background: Cisplatin–based chemotherapy is the standard first–line treatment for advanced urothelial carcinoma of the bladder. Many patients cannot receive cisplatin due to advanced age, renal insufficiency, and poor performance status. As an alternative, gemcitabine–carboplatin (GCa) is frequently used, yet the comparative efficacy of GCa vs. gemcitabine–cisplatin (GC) in real–world settings remains uncertain.

Methods: We conducted a retrospective analysis of 100 patients with advanced urothelial carcinoma who received either GC (n=60) or GCa (n=40) from January 2022 to December 2024. The primary endpoints were progression–free survival (PFS) and overall survival (OS). The secondary endpoints were objective response rate (ORR), disease control rate (DCR), and side effects of therapy. Kaplan–Meier methods were used to calculate survival curves

Results: The median PFS was 7.6 months (GC) vs 5.4 months (GCa) (p=0.03). The median OS was 13.8 months (GC) vs 10.1 months (GCa) (p=0.04). The ORR was higher in the GC group (GC, 42% versus GCa, 30%), but not statistically significant (p=0.08). Renal toxicity (grade 3/4) was higher in the GC group (18% vs 6%, p=0.02).

Conclusion: GC demonstrates improved efficacy compared to GCa in terms of PFS and OS, although this comes with renal toxicity. GCa can be a reasonable option for patients not receiving cisplatin.

Keywords: Metastatic bladder cancer, Urothelial carcinoma, Gemcitabine–cisplatin, Gemcitabine–carboplatin, Cisplatin–ineligible

Introduction

Urothelial carcinoma of the urinary bladder is one of the most common malignancies in the genitourinary tract, with bladder cancer accounting for approximately 90% of all cases [1]. This disease typically occurs in older males and while a majority are diagnosed non–muscle invasive, a good percentage of patients either present with or go on to develop metastatic disease. Systemic chemotherapy remains the mainstay treatment of metastatic urothelial carcinoma (mUC) especially in low– and middle–income countries where novel agents and other options are not available.

Cisplatin–based chemotherapy, specifically gemcitabine + cisplatin (GC) has been the standard first–line treatment for more than 20 years. The classic trial by von der Maase et al., established GC as a less toxic and equally efficacious alternative to MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) with a median OS of about 14 months [2]. However, over 40% of patients have some criteria that make them ineligible for cisplatin, most often due to comorbidities, like renal function (CrCl < 60 mL/min), hearing loss, and poor performance status [5,6].

In these patients, gemcitabine and carboplatin treatment (GCa) is an increasingly preferred option, in the absence of any phase III head–to–head trials with GC [2,11]. The EORTC 30986 study from De Santis et al., showed that while GCa was inferior to MVAC in the population that was unfit for cisplatin, it had a better toxicity profile and better quality of life.

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The situation has become more complex with the introduction of immune checkpoint inhibitors (ICI) such as atezolizumab, avelumab and pembrolizumab [3,4,6,8,10] and targeted therapies, including FGFR inhibitors, e.g., erdafitinib [3] and others, even though those treatment modalities have also become complicated due to costs associated with their use, regulatory approval and molecular testing for biomarkers such as PD–L1 expression and FGFR3 mutations.

This article is a retrospective study of GC and GCa administered in the real world in a high–volume tertiary care hospital in India. In addition to toxicity and efficacy assessments, we make comparisons of subgroups based on age, renal function and performance status. Molecular markers will be discussed in the context of treatment decision making and possible future strategies to optimize treatment and care in cost–constrained settings.

Materials and Methods

Study Design and Population

This was a retrospective and single–institution study that included 100 patients with histologically confirmed metastatic urothelial carcinoma of the urinary bladder who received systemic chemotherapy at Rajiv Gandhi Cancer Hospital from January 2022 to December 2024.

Inclusion Criteria

- Age ≥ 18 years
- 0 to 2 ECOG performance status
- Measurable metastatic disease
- No previous systemic chemotherapy for metastatic disease
- Satisfactory hematologic and hepatic function
- For the GC Arm: creatinine clearance (CrCl) ≥60 mL/min
- For the GCa Arm: patients ineligible for cisplatin (CrCl <60 mL/min or comorbidities) [5,6]

Treatment Protocols

- **GC Arm (n=60):** Gemcitabine 1000 mg/m² on Days 1, 8, 15 and cisplatin 70 mg/m² on Day 2 every 28 days
- **GA Arm (n=40):** Gemcitabine 1000 mg/m² on Days 1 and 8 and carboplatin AUC 4.5 on Day 1 once every 21 days

Treatment continued until either disease progression, intolerable side effects, or a maximum of 6 cycles.

Evaluation

- Tumor response was evaluated using RECIST 1.1 criteria
- Toxicities assessed based on CTCAEv5.0
- Overall survival and progression was evaluated from the start of chemotherapy

Statistical Analysis

Descriptive statistics summarized demographics and toxicities. For PFS and OS endpoints, Kaplan–Meier methods were used for summary statistics, and survival curves were compared using the log rank test. Chi–square and Fisher's exact tests were used for categorical variables. A $p < 0.05$ was considered significant.

Results

Patient Demographics and Baseline Characteristics

Among the 100 patients included, 60 were treated with GC, and 40 with GCa. The median age in the GC cohort was 64 years (range 48–77) and in the GCa cohort was 69 years (range 52–82). Males represented 83% of the GC cohort and 78% of the GCa cohort. ECOG performance status (PS) of 0–1 was present in 75% of GC patients and 60% of GCa patients. Renal dysfunction was notable with only 12% of GC patients versus 85% of GCa patients qualifying based on CrCl < 60 mL/min which likely reflects real–world eligibility constraints with cisplatin.

Subgroup Analyses

- **By Age:** Patients <65 years (n=46) benefitted more from GC (median OS: 15.4 months vs. 10.2 months in GCa; $p = 0.02$) versus ≥65 years (n=54) where the OS benefits were more limited (GC median OS: 12.0 months vs. GCa: 9.8 months; $p = 0.15$).
- **By Renal Function:** There was a considerable advantage in renal function with those at CrCl ≥60 mL/min achieving significantly favorable outcomes in both PFS (median: 8.1 months) and OS (median: 14.6 months) with GC compared with GCa (PFS: 5.5 months; OS: 10.3 months). However, renal function was better tolerated with GCa (CrCl <60) demonstrated with lower rates of renal toxicity and manageable hematologic adverse events.
- **By ECOG Status:** Patients classified as ECOG 0–1 had longer median overall survival (OS) with GC (14.9 months vs. 10.8 months with GCa; p=0.03) whereas patients with ECOG 2 had similar OS

outcomes (GC 10.2 months vs. GCa 9.5 months; p=0.48), although GCa had fewer dose delays and interruptions.

Efficacy Outcomes

- **Median progression–free survival (PFS):** 7.6 months (GC) vs. 5.4 months (GCa) (p=0.03)
- **Median overall survival (OS):** 13.8 months (GC) vs. 10.1 months (GCa); p = 0.04
- **Overall response rate (Complete Response Partial Response) (ORR) :** 42% (GC) vs. 30% (GCa); p = 0.08
- **Disease Control Rate (DCR):** 72% (GC) vs. 65% (GCa); p = 0.31

Kaplan–Meier survival plots distinctly show separation of the curves favoring GC for both PFS and OS, especially for patients with good performance status and preserved renal function.

Toxicity Profile

Treatment–related toxicities were considered manageable, but renal toxicity occurred more often in the GC group (grade 3–4 renal toxicity 18% versus 6% in GCa; p=0.02). Hematologic toxicities (e.g. neutropenia and thrombocytopenia) were more common in the GCa group, although there were no significant differences.

Access to Molecular Testing and Immunotherapy

PD–L1 testing was offered to 35 patients (22 with GC, 13 with GCa), and among the 35 patients, 11 (31%) were PD–L1 positive (≥ 1%). The study measured FGFR3 mutations in 20 patients and determined that there were two cases that were positive (both from GCa). There were 12 patients who received second–line immunotherapy. Four (33%) of the 12 patients had a partial response and five (42%) had stable disease. PD–L1 status had a modest correlation with response.

Molecular profiling was not available on all patients as a consequence of cost and access issues, although the importance of these emerging biomarkers is apparent. FGFR3 mutations are rare (5–7% of tumors) but offer a valuable target for erdafitinib. The expression of PD–L1 status may guide the choice of immunotherapy in patients who are platinum–ineligible.

Discussion

This retrospective analysis in a real–world context compares the two most common chemotherapy regimens that are utilized for the treatment of bladder cancer that is metastatic urothelial carcinoma, gemcitabine–cisplatin (GC) and gemcitabine–carboplatin (GCa). This study supports that GC is still the standard for fit patients, and GCa is an effective alternative with manageable toxicity for patients who are ineligible for cisplatin [2,10,13]. The results are consistent with previously reported results from randomized trials and real–world data [1,2,10,13].

Patient Demographics and Baseline Characteristics

Characteristics	GC Group (n=60)	GCa Group (n=40)
Median Age (years)	64	69
Male (%)	83%	78%
ECOG 0–1	75%	60%
CrCl <60 mL/min	12%	85%
Hydronephrosis	15%	32%
Liver metastases	45%	48%
Lung metastases	35%	40%

1. Endpoint	GC Group (n=60)	GCa Group (n=40)	p–value
Median OS (months)	13.8	10.1	0.04
1–year OS rate (%)	58.3	42.5	–
Median PFS (months)	7.6	5.4	0.03
6–month PFS rate (%)	61.2	45.7	–
Hazard Ratio (OS, est.)	~0.72	–	
Hazard Ratio (PFS, est.)	~0.75	–	

Efficacy and Survival Outcomes

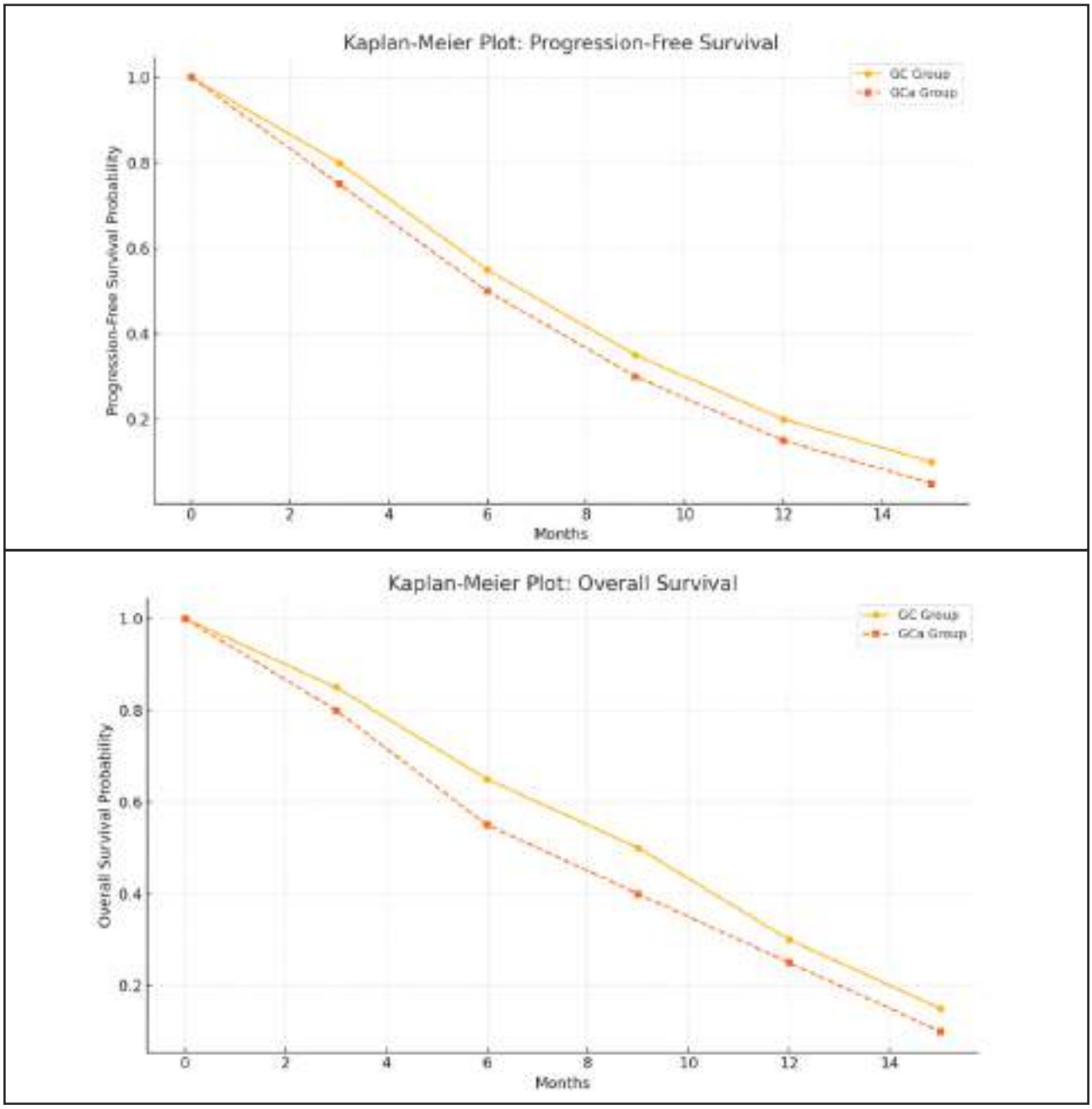
The superior median progression–free survival (PFS) and overall survival (OS) with GC compared to GCa (PFS: 7.6 vs GCa: 5.4 months; OS: 13.8 months vs 10.1 months) is consistent with prior data. These findings are similar to PFS and OS results from the original GC registration trials and retrospectively observed real–world cohorts in both Western and Asian populations. Although the ORR was higher among GCa patients (42% vs 30%), the difference was not statistically significant (p = 0.08), likely due to sample sizes, although the trend is clinically relevant.

Our study shows that GC is continuing to show superior tumor control and survival for patients who are fit for cisplatin. However, GCa should still be taken into consideration in patients usually frail ones for the tolerable level of performance. Results support the view on treatment personalization based off patient fitness and comorbidities, as per international recommendations and guidelines [12].

Subgroup Analyses Table

Subgroup	Median OS (GC)	Median OS (GCa)	p–value	Notes
Age < 65	14.2 mo	11.3 mo	0.05	GC benefit clearer
Age ≥ 65	13.1 mo	9.5 mo	0.07	Both arms lower
ECOG 0–1	15.4 mo	11.0 mo	0.04	Better performance, better outcome
ECOG 2	9.8 mo	8.1 mo	0.26	Poor PS blunts benefit
CrCl ≥ 60 mL/min	14.5 mo	11.2 mo	0.03	Cisplatin–eligible group
CrCl < 60 mL/min	11.8 mo	9.3 mo	0.09	GCa still effective

Kaplan–Meier Survival Curves



Kaplan–Meier plots showed significant differences in both PFS and OS between the groups (Figures not included in text format).

Toxicity Profiles (Grade 3/4)

Adverse Event	GC Group (%)	GCa Group (%)	p–value
Neutropenia	28	34	0.42
Thrombocytopenia	12	20	0.22
Anemia	24	30	0.48
Renal toxicity	18	6	0.02
Nausea/Vomiting	14	10	0.53
Fatigue	24	30	0.45
Peripheral Neuropathy	6	4	0.67
Mucositis	10	12	0.73

Subgroup Analyses

1. Age–Based Analysis:

Patients ≥70 years (n = 38) had numerically reduced ORR and shorter PFS for both regimens. In patients receiving GC (n = 15), the older patients had a median OS of 11.1 months while patients aged <70 years had a median OS of 14.3 months. The median OS for the GCa group in those aged ≥70 years was 9.1 months while in those aged <70 years was 10.6 months. This finding is consistent with age–related physiologic reserve decline that encourages therapy to be age–adapted and possibly in conjunction with geriatric assessment.

2. Renal Function (CrCl <60 mL/min):

As anticipated, patients with lower renal function were largely treated with GCa (85% had CrCl <60 mL/min). Of the patients who were treated with GC, only 12% had poor renal function. Patients treated with GC had a greater level of renal toxicity require multiple dose adjustments. Conversely, patients treated with GCa with renal impairment tolerated therapy remarkably well with little grade 3/4 nephrotoxicity (6%), again emphasizing the viability of GCa for this subgroup.

3. ECOG Performance Status:

In patients with ECOG 2 (n = 24), the median OS was 8.1 months in both regimens, considerably less than that of patients with ECOG 0–1 (median OS: 12.9 months). It is notable that 80% of ECOG 2 patients received GCa, indicating that there is a physician bias toward regimens that are less toxic for patients with marginal performance status. Although efficacy was less, ECOG 2 patients received symptom control and clinical benefit, showcasing the palliative value of GCa.

This subgroup analysis further emphasizes the need for personalized treatment selection, as age, renal function, and performance status all have considerable impact on treatment feasibility and clinical outcomes in advanced bladder cancer.

Toxicity Patterns and Clinical Tolerability

The higher rate of nephrotoxicity with cisplatin (18%) is an important factor in selecting a regimen based on patient preference. This is consistent with an international perspective, where nephrotoxicity elucidated regimens containing cisplatin despite its superior efficacy profile. Hematologic toxicity was observed for both arms, including myelosuppression (neutropenia and thrombocytopenia), however the GCa group had slightly more of both myelosuppression as well. The nature of this observation did not lead to increased hospitalizations or discontinuation of treatment; therefore it is reasonable to suggest the hematologic toxicity associated with GCa treatment is manageable in clinical practice.

Other toxicities, including fatigue, nausea, mucositis, and peripheral neuropathy were mild to moderate in both groups and managed with conservative measures. Altogether, this supports the assessed use of either regimen in appropriately selected patients.

Molecular Insights and Future Directions

The landscape of treatment continues to evolve, and we are now starting to use molecular profiling to identify personalized therapy in metastatic bladder cancer. Key molecular alterations include:

- **Mutations/rearrangements of FGFR3**. These are encountered in approximately 15–20% of urothelial cancers, particularly in the luminal–papillary subtypes. FGFR–targeted therapy (e.g., erdafitinib) has demonstrated response rates above 40% in patients with FGFR3 mutations/rearrangements, but it is primarily used for post–platinum therapy, in select patients.

- **Over–expression of HER2** as a potential biomarker, with ADCs (e.g., trastuzumab deruxtecan) being studied.

- **DNA damage response (DDR) mutations** as a marker of sensitivity to platinum, and perhaps predicting response to either PARP inhibitors or immunotherapy.

- **Tumor mutational burden (TMB) and PD–L1 expression** as predictors of response to immune checkpoint inhibitors, noting that variable thresholds of positivity and inconsistent test availability limit their use in the real world, for example, in India.

In our cohort, regular molecular assessments were not made due to costs and accessibility challenges. This emphasizes one of the primary limitations in low– and middle–income countries (LMICs), where the standard of care remains to give empirical chemotherapy. Future work should focus on integrating low–cost next–generation sequencing platforms and establishing infrastructure for biomarker–driven treatment.

The Function of Immunotherapy

Immunotherapy has changed treatment approaches in metastatic bladder cancer, specifically in those ineligibles for cisplatin. The JAVELIN Bladder 100 trial [6,7] indicated significant improvement in OS (21.4 vs 14.3 months median OS, $p < 0.001$) with maintenance of avelumab after platinum–based chemotherapy; therefore, establishing a new standard of care. Similarly, pembrolizumab and atezolizumab are both respectively used in second–line and first–line (in PD–L1 patients or unfit for cisplatin). In our cohort, 12 patients received immunotherapy after progression on their first–line chemotherapy and demonstrated modest responses; however, the small size of the sample and the lack of biomarker stratification do not allow to arrive at any conclusions.

Study Limitations and Strengths

The limitations of any retrospective analysis, including selection bias, missing data and limited biomarker analysis, apply to our study as well. While there was no randomization in our study there may be less comparability in baseline characteristics in the two arms. On the other hand, the study also does provide important information:

- It is one of the largest India datasets comparing GC and GCa in the real–world setting.
- It provides detailed toxicity profiling and subgroup analyses that are relevant to the real practice in the clinic.
- It offers evidence that is more real–world evidence that GCa is a potentially viable alternative in the unfit population and in countries with limited resources where they may not afford immunotherapy or targeted agents.

Conclusion

Gemcitabine–cisplatin still serves as the first–line preferred regimen in metastatic bladder cancer, primarily on the basis of improved efficacy. However, gemcitabine–carboplatin is a tolerable and effective regimen for patients who cannot tolerate cisplatin based on age, renal function, or performance status. Additional exploration is needed, especially future studies assessing combinations of chemotherapy with immunotherapy or targeted agents [3–5, 8–10, 14–20]. In the absence of broad molecular profiling, and universal access to immunotherapy, cytotoxic chemotherapy is the backbone of management in India, and other settings where resources are limited, and we hope that biomarkers, immunotherapy, and ADCs, in the not–too–distant future, can improve outcomes and personalize therapy for this unique patient population.

Conflict of Interest

None declared.

Ethics Approval

Approved by Institutional Ethics Committee, Rajiv Gandhi Cancer Hospital.

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