# Gemcitabine versus cisplatin in concurrent radio chemotherapy for bladder preservation

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**Abstract: Purpose:** The aim of this prospective study was to compare the efficacy and toxicities of gemcitabine to cisplatin as a radio sensitizer in trimodality treatment of bladder transitional cell carcinoma. **Methods:** It was a prospective study on 100 patients with bladder TCC, clinical stage T2 or T3 N0 M0 who underwent concurrent radio chemotherapy after maximum safe trans-urethral resection. Patients were divided into 2 groups: gemcitabine group, received weekly doses of gemcitabine 125mg/m$^2$, and cisplatin group, received weekly doses of cisplatin 40mg/m$^2$ concurrently with 66 Gy of conventional radiation therapy. **Results:** Disease free survival in gemcitabine group was 79.4%, while in cisplatin group was 77.6% with insignificant differences. All patients in cisplatin group tolerated treatment protocol completely, while six patients in gemcitabine group could not completed their weekly gemcitabine doses because of grade III gastrointestinal toxicity. **Conclusions:** Gemcitabine is a reasonable option in trimodality treatments in urinary bladder preservative strategies.
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## 1. Introduction

Cancer bladder is the second male cancer in Egypt, and the fourth in United States and Europe (1-3).Although, radical cystectomy still considered as a standard especially among urologists, it complicated bypsychological, physical, sexual, morbidity, and bad effects on quality of life. Trimodality treatment, using concurrent radio chemotherapy after maximum safe transurethral resection of the tumor, is the most effective bladder preserving treatment modality (4).There is no will organized randomized trial compared cystectomy to trimodality treatment but only retrospective and prospective non-randomized studies are present. These trials had several sources of bias, as there are multiple confounding variables against trimodality treatment including clinical staging that under-stage 50% of patients,[5] advanced age, worse performance status and co-morbidities. Despite the above confounding variables, a search of English medical literature in PubMed from 1990 until 2013 was carried out, they compared 3,131 patients received trimodality treatment to 10,256 patients underwent radical cystectomy. They found median 5-year OS rate of 57% in patients undergoing trimodality treatment, that was significantly better than the 51% rate in patients underwent radical cystectomy alone (p=0.02) (6). Cisplatin is the recommended radiosensitizer in trimodality treatment (4, 7); however it has significant nephrotoxicity, myelosuppression and emetogenicity. Gemcitabine is proved to be a potent radio sensitizer in vitro, and it had a demonstrated efficacy on cancer bladder cells,[8] in addition gemcitabine concurrently with radiotherapy is well tolerated in bladder cancer patients (9, 10).This is a non-randomized prospective study compared the efficacy and toxicity of gemcitabine to cisplatin as a radio sensitizer in trimodality treatment of bladder transitional cell carcinoma.

## 2. Materials and methods

In a non-randomized, prospective study of 100 patients treated at South Egypt Cancer Institute and Military Cancer Center. The ethics committee of South Egypt Cancer Institute approved this study, and all patients signed written consent. Patients to be eligible must have transitional cell carcinoma (TCC) of the urinary bladder, clinical stage T2 or T3 N0 M0, maximum safe trans-urethral resection of bladder tumor, performance status $\leq$ 1, normal laboratory values and treated by concurrent radio chemotherapy that started within 6 weeks from the resection, cisplatin or gemcitabine used as a radio sensitizer (11). Exclusion criteria were multi-centric tumors and patients previously received interavesical BCG, chemotherapy, or pelvic irradiation. Eligible patients distributed between two groups, gemcitabine and cisplatin group. All patients planned to receive weekly doses of gemcitabine 125mg/m$^2$ (gemcitabine group)or cisplatin 40mg/m$^2$ (cisplatin group) given within two hours before Saturday radiation session. All patients received conformal radiotherapy. Pelvis clinical target volume (CTV-pelvis) was whole bladder, prostate and prostatic urethra (in men), and

pelvic lymph nodes (internal and external iliac, and obturator). CTV-bladder included any gross tumor volume (GTV) and whole bladder. The organs at risk (OAR) were rectum, small intestine, and femoral heads. Radiotherapy delivered in 2 phases; phase I, 46 Gy in 23 fractions given to PTV-pelvis, and phase II, 20 Gy in10 fractions to PTV-bladder. Regarded OAR, V50 for femoral heads <5%,and V55 for rectum <50%.During radiotherapy, we did clinical and laboratory evaluation by complete blood counts before each chemotherapy administration, while blood electrolytes, and creatinine every 3 weeks. After radiotherapy, patients underwent clinical evaluation by history and physical examination monthly during first 6 months, every 2 months during the second 6 months, and every 3 months thereafter. They did abdominal pelvic CT or MRI and cystoscopy every 3 months in the first year, then every 4 months in the second year then twice a year subsequently, and chest imaging twice a year for the first 2 years and then annually. Complete remission (CR) defined as no measurable disease that confirmed by cystoscopy and biopsy. In case of persistent invasive TCC, patients underwent salvage cystectomy. The statistical analysis included chi-square test for comparing percentages. Disease free survival (DFS) was calculated according to Kaplan-Meier actuarial method from the time of diagnosis (12). Log rank test used to compare survival rates. The p-values were double-sided and ≤0.05 was the level of significance. We reported toxicity from radiotherapy and chemotherapy according to Common Toxicity Criteriafor Adverse Events (CTCAE) version 3.0 (13).

## 3. Results

Patient's characteristics listed in Table 1; both gemcitabine and cisplatin group were matched and no statistical significant regarded different characteristics.

### 3.1. Treatment tolerability

All patients completed their radiotherapy course up to 66Gy in both groups, however six patients did not receive their weekly gemcitabine doses completely as follow; 2 patients had three weekly doses, 2 patients had four doses and 2patients had five gemcitabine doses. All six patients stopped chemotherapy because of grade III gastrointestinal toxicity.

### 3.2. Treatment response

Patients underwent cystoscopic assessments at 3 months (Table 2), that revealed no tumor (CR) in 41 patients (82%) in gemcitabine group, and 36 patients (72%) in cisplatin group with insignificant differences (p=0.34). Patients who had residual tumor after 3 months underwent salvage cystectomy (9 patients in gemcitabine group, and 14 patients in cisplatin group).

### 3.3. Follow up

During follow up, five patients in gemcitabine group developed invasive recurrences at 6, 10, 15, 21, and 24 months; two of them were metastatic. Six patients in cisplatin group developed invasive recurrences occurred at 15, 16, 20, and 23 months of follow up. All patients with invasive non-metastatic recurrences underwent salvage cystectomy. We detected four non-invasive recurrences; two in each group, and all became free of tumor after interavesical BCG. Two year disease free survival in gemcitabine group was 79.4 ± 7.1 while in cisplatin group was 77.6 ± 8.6 (Table 3) with insignificant difference (p=0.3) (Figure 1).

**Table 1.** Patient characteristics

| Variable | | Gemcitabine | Cisplatin | p-value |
|---|---|---|---|---|
| Age | ≥60 | 19 | 23 | 0.54 |
| | <60 | 31 | 27 | |
| Sex | Male | 45 | 43 | 0.75 |
| | Female | 5 | 7 | |
| Bilharziasis | Yes | 13 | 18 | 0.39 |
| | No | 37 | 32 | |
| Hydronephrosis | Yes | 26 | 16 | 0.07 |
| | No | 24 | 34 | |
| Tumor size | T2 | 29 | 24 | 0.42 |
| | T3 | 21 | 26 | |
| TUR | Complete | 19 | 20 | 1 |
| | Incomplete | 31 | 30 | |
| Grade | G2 | 36 | 30 | 0.29 |
| | G3 | 14 | 20 | |

Disease specific survival was 100% for all patients. All patients in cisplatin group tolerate treatment protocol completely, while six patients in gemcitabine group could not complete their weekly gemcitabine doses because of grade III gastrointestinal toxicity, incidence of acute toxicity listed in Table 4. Patients in gemcitabine group had all grades of toxicity; grade III toxicity detected as diarrhea in 12% and anemia in 10%; grade I-II mainly cystitis in 100%, diarrhea in 62%, and proctitis in 38% of patients. Patient in cisplatin group had no grade III and only grade I-II toxicity, mainly cystitis in all patients, diarrhea in 60% and vomiting in 40%.

**Table 2.** ***Cystoscopic assessment after 3 months***

| Variable | | Gemcitabine | Cisplatin | p-value |
|---|---|---|---|---|
| CR | Yes | 41 (82%) | 36 (72%) | 0.34 |
| | No | 9 (18%) | 14 (28%) | |

**Table 3.** Two year disease free survival

| Variable | Gemcitabine | Cisplatin | P value |
|---|---|---|---|
| 2-year DFS (%) | 79.4±7.1 | 77.6±8.6 | 0.83 |

**Table 4.** Incidence of acute toxicity

| Variable | Grade I and II | | Grade III | |
|---|---|---|---|---|
| | Gemcitabine | Cisplatin | Gemcitabine | Cisplatin |
| Anemia | 17 (34%) | 12 (24%) | 5 (10%) | 0 |
| Diarrhea | 31 (62%) | 30 (60%) | 6 (12%) | 0 |
| Proctitis | 19 (38%) | 10 (20%) | 0 | 0 |
| Vomiting | 13 (26%) | 20(40%) | 0 | 0 |
| Cystitis (dysuria and/or frequency) | 50 (100%) | 50 (100%) | 0 | 0 |

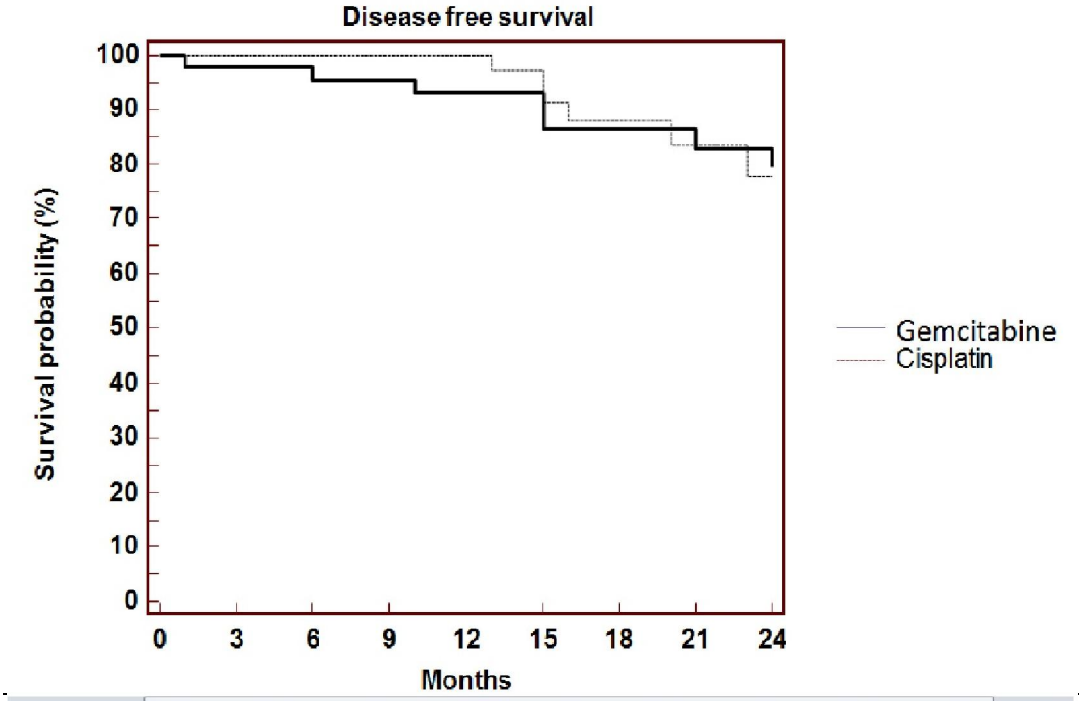


**Figure 1. Disease free survival for gemcitabine and cisplatin group**

**4. Discussion and conclusions**

In efforts to overcome the toxicity of cisplatin during trimodality bladder preservative strategies, gemcitabine is an attractive option especially it is well known radio sensitizer, has no significant cumulative effects on renal function [14]and has potent efficacy in TCC bladder. We perform this study to compare gemcitabine to cisplatin, the slandered radio sensitizer, regarded its efficacy and toxicity. According to our study, gemcitabin considered as efficient as cisplatin as there is no statistical significant regarding response, toxicity, and survival. Cystoscopy after 3 months revealed no tumor in 82% of patients in gemcitabine group, and 72% in cisplatin group without any statistical significant differences that is comparable to other trimodality treatment studies (15, 16). All patients in cisplatin group tolerated the treatment, similar to other studies (17), while six patients in gemcitabine group developed Grade III gastrointestinal toxicity that cannot complete their weekly chemotherapy doses. Gemcitabine toxicity is comparable to a study using gemcitabineas a radio sensitizer tri-modality bladder preservative strategy (18). At median 2 year, Disease free survival in gemcitabine group was 79.4%while in cisplatin group was 77.6% with statistically insignificant difference. These figures are comparable to that reported by most clinical trials studied in trimodality treatments (19, 20). Regarding gemcitabine toxicity, we can observe: 1) it is not affect renal function and can used in renal impairment, the common associated complication in bladder cancer, 2) do not affect the response rate and survival, and 3) toxicity that affect weekly gemcitabine schedules were gastrointestinal toxicity that can be reduced with modern radiotherapy techniques such as IMRT, VMAT (21), and adaptive radiation, in particularly online adaptive radiotherapy (22), that still investigational in bladder cancer. Although this is non-randomized study; however, limited number of patients is a limiting issue to our study, and we could conclude that gemcitabine is a reasonable option in trimodality treatments in bladder preservative strategies.

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**References:**

1. Ibrahim, A. S., Khaled, H. M., Mikhail, N. N., Baraka, H. & Kamel, H. Cancer incidence in egypt: results of the national population-based cancer registry program. J. Cancer Epidemiol. 2014, 437971 (2014).
2. Ferlay, J. et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur. J. Cancer 49, 1374–403 (2013).
3. Siegel, R., Naishadham, D. & Jemal, A. Cancer statistics, 2013. CA. Cancer J. Clin.63, 11–30 (2013).
4. Arcangeli, G., Arcangeli, S. & Strigari, L. A systematic review and meta-analysis of clinical trials of bladder-sparing trimodality treatment for muscle-invasive bladder cancer (MIBC). Crit. Rev. Oncol. Hematol. 94, 105–15 (2015).
5. Gray, P. J. et al. Clinical-pathologic stage discrepancy in bladder cancer patients treated with radical cystectomy: results from the national cancer data base. Int. J. Radiat. Oncol. Biol. Phys.88, 1048–56 (2014).
6. Arcangeli, G., Strigari, L. & Arcangeli, S. Radical cystectomy versus organ-sparing trimodality treatment in muscle-invasive bladder cancer: A systematic review of clinical trials. Crit. Rev. Oncol. Hematol.95, 387–96 (2015).
7. NCCN Clinical Practice Giudlines in Oncology. Bladder Cancer, version 2.2015. 21 (2015). at http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
8. Sangar, V. K., Cowan, R., Margison, G. P., Hendry, J. H. & Clarke, N. W. An evaluation of gemcitabines differential radiosensitising effect in related bladder cancer cell lines. Br. J. Cancer 90, 542–8 (2004).
9. Sangar, V. K. et al. Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. Int. J. Radiat. Oncol. Biol. Phys. 61, 420–5 (2005).
10. De Santis, M. et al. Combined chemo radiotherapy with gemcitabine in patients with locally advanced inoperable transitional cell carcinoma of the urinary bladder and/or in patients ineligible for surgery: a phase I trial. Ann. Oncol.25, 1789–94 (2014).
11. Oken, M. M. et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J. Clin. Oncol.5, 649–55 (1982).
12. Kaplan, E. L. & Meier, P. Nonparametric Estimation from Incomplete Observations. J. Am. Stat. Assoc. (2012). at http://www.tandfonline.com/doi/abs/10.1080/01621459.1958.10501452.
13. Common Toxicity Criteria, Version 3. Available from:http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
14. Gietema, J. A., Groen, H. J., Meijer, S. & Smit, E. F. Effects of gemcitabine on renal function in patients with non-small cell lung cancer. Eur. J. Cancer 34, 199–202 (1998).

15. Gamal El-Deen, H. S. Initial results of retrospective study: preoperative transurethral excision plus chemotherapy and radiation therapy and trial of bladder preservation. J. Egypt. Natl. Canc. Inst. 19, 133–46 (2007).
16. Aboziada, M. A., Hamza, H. M. & Abdlrahem, A. M. Initial results of bladder preserving approach by chemo-radiotherapy in patients with muscle invading transitional cell carcinoma. J. Egypt. Natl. Canc. Inst. 21, 167–74 (2009).
17. Lee, C.-Y. et al. Trimodality bladder-sparing approach without neoadjuvant chemotherapy for node-negative localized muscle-invasive urinary bladder cancer resulted in comparable cystectomy-free survival. Radiat. Oncol. 9, 213 (2014).
18. Kent, E. et al. Combined-modality therapy with gemcitabine and radiotherapy as a bladder preservation strategy: results of a phase I trial. J. Clin. Oncol.22, 2540–5 (2004).
19. Shipley, W. et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 60, 62–67 (2002).
20. Oh, K. S. et al. Combined-modality therapy with gemcitabine and radiation therapy as a bladder preservation strategy: long-term results of a phase I trial. Int. J. Radiat. Oncol. Biol. Phys. 74, 511–7 (2009).
21. Foroudi, F. et al. A dosimetric comparison of 3D conformal vs intensity modulated vs volumetric arc radiation therapy for muscle invasive bladder cancer. Radiat. Oncol. 7, 111 (2012).
22. Foroudi, F. et al. Online adaptive radiotherapy for muscle-invasive bladder cancer: results of a pilot study. Int. J. Radiat. Oncol. Biol. Phys. 81, 765–71 (2011).

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