Gemcitabine Single Agent for Recurrent Post Bladder Preservation Therapy and in Metastatic Transitional Cell Carcinoma of Urinary Bladder in Elderly Patients with Renal Impairment

Haider Y. Shukur

Middle Euphrates Cancer Center of Clinical Oncology (MECC), Faculty of Medicine, Ibn Hayyan Medical University, Iraq

Abstract  Purpose: The objectives of the study are to evaluate efficacy (ORR, PFS, & OS) and toxicity of single-agent gemcitabine in recurrent post conservative therapy and in the metastatic transitional cell carcinoma of the urinary bladder in elderly patients with a renal impairment. Patients and Methods: Between March 2014 and September 2016, Fourteen patients have recurrent post conservative therapy & in metastatic transitional cell cancer of the urinary bladder in elderly patients with renal impairment were included to receive single-agent gemcitabine (1,000 mg/m²) administered weekly times three on a 4-week cycle. The median age was 74.5 years. The majority of patients (57.2%) have metastatic disease at diagnosis also a majority of patients (57.2%) have a solitary metastatic disease. The median overall treatment period was 14 weeks (range: 4-24 weeks). Results: Overall response rate was 35.7% (CR 7.1% + PR 28.6%). Median-Progression Free Survival was 20 weeks (95% CI: 8.313-31.687). Median Overall survival rates were 40 weeks (95% CI: 28.313-51.687). 50% of patients experienced at least one grade 1 or 2 neutropenia and 71.5 % of patients developed thrombocytopenia and no patient (0 %) required hospitalization during therapy for neutropenic fever or dehydration . 50% patients required treatment delayed at least one week due to treatment toxicity. Conclusion: The single agent Gemcitabine had significant improvement in response rate, progression-free survival and overall survival with good tolerance and manageable toxicity.

Keywords  Recurrent Bladder Cancer, Transitional Cell Carcinoma, First-line Therapy, Gemcitabine, Chemotherapy, Metastasis

1. Introduction

The incidence of bladder cancer is increasing. An estimated 74,000 new cases of urinary bladder cancer will be diagnosed in the United States (56,320 men and 17,680 women) in 2015. [1]

Bladder cancer, the sixth most common cancer, is three times more prevalent in men than in women in the United States. During the same period, approximately 16,000 deaths (11,510 men and 4490 women) will result from bladder cancer.[2]

Bladder cancers are rarely diagnosed in individuals younger than 40 years of age. Because the median age at diagnosis is 65 years, medical co-morbidities are a frequent consideration in patient management. [3]

The highest incidence is observed in Egypt with 37 cases per 100,000 inhabitants. Smoking is the most implicated risk factor in western countries, followed by other factors such as polycyclic aromatic hydrocarbons and cyclophosphamide. [4]

In East Africa (especially Egypt), chronic infection with Schistosoma haematobium is the most common etiology and is often associated with squamous cell carcinoma. [5]

More than 90% of urothelial tumors originate in the urinary bladder, 8% originate in the renal pelvis, and the remaining 2% originate in the ureter and urethra. Urothelial (transitional cell) carcinomas, the most predominant histological type which represents more than 90% of the cases in the United States, may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra. [6,7]

The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of non-muscle-invasive tumors (epithelium, Ta; lamina propria, T1; or carcinoma in situ, Tis) which is managed with complete transurethral resection of the bladder tumor (TURBT) with or without intravesical therapy where goal of the treatment is directed at reducing recurrences and preventing progression to a more advanced stage. [8]
The second group encompasses the muscle-invasive lesions, which is characterized by a distinct biology which includes the structural or functional loss of tumor suppressor genes such as TP53, Rb and PTEN resulting in more than 50% of cases progressing to the lethal phenotype of metastatic disease and the goal of therapy is to determine if the bladder should be removed or preserved without compromising survival, and to determine if the primary lesion can be managed independently or if patients are at high risk for distant spread requiring systemic approaches to improving the likelihood of cure. [9]

The critical concern of therapy for the third group, consisting of metastatic lesions, is how to prolong quantity and quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The issue remains how to use these agents to achieve the best possible outcome.

2. Patients and Methods

2.1. Patient Eligibility

Eligible patients had histological confirmed transitional cell carcinoma (TCC) of the bladder recurrent post –bladder preservation by TUBR and CCRT & stage IV (Patients either T4 disease, N+ or M1).

2.2. Inclusion Criteria

1) WHO- performance status (WHO-PS) of 0-2
2) Age 60 to 85 years
3) Glomerular filtration rate (GFR) ≥30 ml/min (Cockcroft & Gault formula);
4) Patient with solitary kidney was included
5) Written informed consent had to be given.

2.3. Exclusion Criteria

1) Abnormal biochemistry (i.e., bilirubin 1.3-ULN, alkaline phosphatase 5-ULN, AST/ALT 5-ULN).
2) Patients with other primary malignancy.

2.4. Pretreatment Evaluation Included

CT scan of the chest-abdomen-pelvis, cystoscopy, urinalysis, WHO-PS, weight blood count, and chemistry as well as baseline adverse event (AE) assessment.

2.5. Treatment Schedule

Treatment consisted of gemcitabine (1,000 mg/m2) given as a 30 minutes intravenous infusion in 250 ml glucose 5% administered weekly times three on a 4-week cycle. This treatment was preceded by premedication as antiemetic (dexamethasone 8 mg and 5-HT3 receptor antagonists 8 mg ondansetron), Ranitidine 150 mg and diphenhydramine maleate ampoule all are administered intravenously in 100 ccs normal saline solution over 15 min. just before chemotherapy. In the event of predefined toxic events, treatment delayed was permitted until recovery. Patients discontinued the study in the event of unacceptable toxic effects or evidence of progressive disease, or at their request.

2.6. Dose Adjustment and Dose Modification

Dose adjustments were based on clinical assessment for toxicity and blood count once a week, taken immediately before administration of chemotherapy, and blood chemistry, urinalysis, and GFR calculation carried out once a cycle.

2.7. Gemcitabine was Held For:

WBC <2.0 × 10^9 /l,
ANC <1.0 × 10^9/l or
platelets <50 × 10^9/l or
a GFR <30 ml/min until recovery to a GFR of ≥30ml/ min, any grade 3/4 non-hematological toxicity until recovery to grade ≤2

2.8. Treatment Assessments

Including toxicity and response evaluation:
At the end of third cycles, patients were assessed with physical examination, blood chemistry, blood count, and CT scan of the chest-abdomen and pelvis. Then responding patients complete further three cycles then re-evaluate completely and planned to keep on follow up every 3 months. In other hand, patients with disease progression after third cycles shift to BSC.

3. Statistical Analysis

Data was analyzed using SPSS statistical package version 17.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as median and range as appropriate. Qualitative data were expressed as a percentage. The survival curves were estimated using the Kaplan–Meier technique.

4. Results

Between March 2014 and September 2016, 14 patients were enrolled in our center (MECC). The median follow-up was 62 weeks (range 4–120 weeks). All eligible patients had predominant transitional cell carcinoma of the urinary bladder and met the inclusion criterion. The final analysis was conducted in September 2016. Median age was 74.5 years (range: 60–85 years), with 28.6% older than 80 years. Two (14.3%) of our patients were female, while twelve (85.8%) patients were male. Three of our patients (21.4%) have WHO performance state of zero, while six (42.9%) patients have WHO performance state of one and remaining
five (35.7%) patients have WHO performance state of two. Six (42.9%) of our patients were progressed after bladder preservative therapy and eight (57.2%) patients have a metastatic disease at diagnosis. Baseline demographic and clinical characteristics are listed in Table (1). Two (14.3%) have pelvic disease recurrent; four (28.6%) patients have liver metastasis, and two (14.3%) patients have pulmonary metastasis. Five (35.7%) patient have bone metastasis and only one (7.1%) patient had supraclavicular lymph node metastasis. Furthermore, in our study, eight (57.2%) patients have a solitary site of metastasis while six (42.8%) patients have multiple sites of metastasis.

**Table 1.** The detailed patient characteristics are listed in Table 1.

| Characteristic                        | No. of patients | %     |
|---------------------------------------|-----------------|-------|
| Age Yr                                | 74.5 (60-85)    | 28.3  |
| Median Age ≥ 80                        | 4               | 28.3  |
| Sex                                   |                 |       |
| Female                                | 2               | 14.3  |
| Male                                  | 12              | 85.8  |
| WHO-Performance state                 |                 |       |
| 0                                     | 3               | 21.4  |
| 1                                     | 6               | 42.9  |
| 2                                     | 5               | 35.7  |
| Recurrent post conservative therapy   | 6               | 42.9  |
| Metastatic disease                    | 8               | 57.2  |
| Sites of recurrent /metastasis        |                 |       |
| Pelvis                                | 2               | 14.3  |
| Liver                                 | 4               | 28.6  |
| Lung                                  | 2               | 14.3  |
| Bone                                  | 5               | 35.7  |
| Distant LN (supraclavicular)          | 1               | 7.1   |
| No. of metastatic sites               |                 |       |
| Solitary                              | 8               | 57.2  |
| Multiple                              | 6               | 42.8  |

5. Treatment Delivery

Three (21.4%) patients received ≤ three cycles, and eleven (78.5%) patients completed 4-6 cycles chemotherapy. The total number of chemotherapy cycles was 67 cycles, also there were seven (50%) patients have delayed cycle by ≥ 1 week. (Table 2).

**Table 2.** Treatment delivery, n = 14

| Number of cycles | Number of patients | %  |
|------------------|--------------------|----|
| ≤3               | 3                  | 21.4|
| 4-6              | 11                 | 78.5|
| Total number of cycles | 67            |     |
| Number of cycles delayed by≥ 1 week | 7     | 50  |

6. Efficacy

One patient (7.1%) had a complete response (CR) proved by CT scan & cystoscope evaluation. Four (28.6%) patients have a partial response (PR). Five (35.7%) patients obtained stable disease (SD) and 4 (28.6%) patients have progressive disease (PD). Objective response rate (ORR) was (35.7%) and clinical benefit rate (CBR) was (71.5%). The median duration of response was 32 weeks (range; 4-60 weeks). The response to therapy is summarized in Table (3). One (7.1%) patient had to be taken off treatment due to disease progression and best supportive care was administered for him then later on died. Three (21.7%) patients were dead, so the final total number of deaths were four (28.6%) patients. Figure (1)

**Table 3.** Objective Response rate, n = 14

| Response                | No. of patients | (%) |
|-------------------------|-----------------|-----|
| Complete remission(CR)  | 1               | 7.1 |
| Partial Response (PR )  | 4               | 28.6|
| Stable Disease (SD)     | 5               | 35.7|
| Progressive Disease (PD)| 4               | 28.6|
| Overall Response Rate (ORR) | 5      | 35.7|
| Clinical Benefit Rate (CBR)| 10   | 71.5|
| Median PFS (weeks)      | 20              |     |
| Median OS (weeks)       | 40              |     |
7. Toxicity

Table 4. Adverse events during treatment, n = 14

| Adverse events                                      | No of Patients | (%)  |
|------------------------------------------------------|----------------|------|
| **Hematological toxicity**                          |                |      |
| • Anemia                                             | 14             | 100  |
| • Neutropenia                                        | 7              | 50   |
| • Thrombocytopenia                                   | 10             | 71.5 |
| • Neutropenic fever                                  | 0              | 0    |
| **Hematological toxicity**                          |                |      |
| • Flu-like symptoms*                                 | 8              | 57.2 |
| • Nausea                                             | 5              | 35.7 |
| • Vomiting                                           | 7              | 50   |
| • Poor appetite                                      | 5              | 36   |
| • Skin rash                                          | 1              | 7.15 |
| • Epistaxis /Bleeding different sites                | 3              | 21.7 |
| • Weight loss                                        | 4              | 28.6 |
| • Protein in urine                                   | 2              | 14.3 |
| • Temporary increases in liver enzymes               | 4              | 28.6 |
| • Others as diarrhea ,weakness, hair loss mouth sores & shortness of breath | 8 | 57.2 |

*(muscle pain, fever, headache, chills, fatigue)

With regard to tolerability, all patients experienced at least one grade 1 or 2 adverse events, grade 2 anemia occurred in 100% of patients. A total 7 out of the 14 patients (50%) experienced at least one grade 1 or 2 neutropenia. Ten (71.5 %) of patients developed thrombocytopenia and no patient (0 %) required hospitalization during therapy for neutropenic fever or dehydration. Seven (50%) patient required treatment delayed at least one week due to treatment toxicity. Flue like was observed in 8 (57.2%) of patients that required simple medication. Five (35.7%) patients developed nausea, while seven (50%) patients developed vomiting. Five (35.7%) patients indicate poor appetite and weight loss less than 5% of baseline weight occurred only in four (28.6%) patients. Three (21.7%) patients have epistaxis or upper/lower GIT bleeding / hematuria. Two (14.3%) patients developed grade one protein urea that needs delaying therapy for one week till recovery. Four (28.6%) patients developed elevating liver enzyme. Eight (57.2 %) patients complain from other different adverse events as diarrhea, weakness, hair loss, mouth sores & shortness of breath. The adverse events profile is shown in the table (4).

8. Survival

Median follow-up was 62 weeks (range 4–120 weeks). 4(28.6%) patients died. Ten (71.4%) patients continue and completed all chemotherapy cycles. The median progression-free survival was 20 weeks (95% CI: 8.313-31.687), figure (2). Regarding overall survival, median OS was 40 weeks (95% CI: 28.313-51.687), figure (3)
9. Correlation Parameters

There is highly significant strong negative correlation between PFS and age, \((r = -0.870)\), and \(P = 0.000\) as showing in the table (5). There is non-significant week negative correlation between PFS and number of metastatic sites, \((r = -0.512)\) and \(P = 0.061\) also there is non-significant week negative correlation between PFS and sites of metastasis, \((r = -0.509)\) and \(P = 0.063\). There is significantly strong negative correlation between PFS and weight loss during treatment, \((r = -0.735)\) and \(P = 0.003\). Finally, there is a significantly strong negative correlation between PFS and elevated liver enzymes, \((r = -0.735)\) and \(P = 0.003\). There is no correlation between PFS and WHO-performance state, \((r = 0.065)\), and \(P = 0.826\). There is no correlation between PFS and grade of disease, \((r = -0.291)\), and \(P = 0.312\). There is no correlation between PFS and recurrent post-bladder preservation, \((r = 0.265)\) and \(P = 0.360\).
On another hand, regarding overall survival correlation, there is highly significant strong negative correlation between OS and age, \((r=-0.849)\), and \(P=0.000\) as showing in the table (5). There is non-significant week negative correlation between OS and number of metastatic sites, \((r = -0.476)\) and \(P=0.122\) also there is non-significant week negative correlation between OS and sites of metastasis, \((r = -0.759)\) and \(P=0.002\). There is a significant strong negative correlation between OS and weight loss during treatment, \((r = -0.759)\) and \(P=0.000\). There is no correlation between OS and WHO-performance state, \((r = 0.016)\), and \(P=0.957\). There is no correlation between OS and grade of disease, \((r= -0.173)\), and \(P = 0.554\). There is no correlation between OS and recurrent post-bladder preservation, \((r = 0.399)\) and \(P=0.157\). There is strong positive correlation between survival outcome and any types of response (CBR), \((r= 0.742)\), and \(P=0.002\). Lastly, there is a strong positive correlation between PFS and OS, \((r=0.921)\) and \(P=0.000\).

**Correlation between PFS and OS with different variables**

| Characteristics                  | PFS          | OS           |
|----------------------------------|--------------|--------------|
|                                  | \(r\) | \(p\) | \(r\) | \(p\) |
| Age                              | -0.870**    | 0.000       | -0.849** | 0.000 |
| WHO-performance state            | 0.065       | 0.826       | 0.016    | 0.957 |
| Grade of disease                 | -0.291      | 0.312       | -0.173   | 0.554 |
| Number of metastatic sites       | -0.512      | 0.061       | -0.433   | 0.122 |
| Metastatic sites                 | -0.509      | 0.063       | -0.476   | 0.085 |
| Recurrent post-bladder preservation | 0.265      | 0.360       | 0.399    | 0.157 |
| Weight loss during treatment     | -0.735**    | 0.003       | -0.759** | 0.002 |
| Elevated liver enzymes           | -0.735**    | 0.003       | -0.759** | 0.002 |
| Clinical benefit rate            | 0.788**     | 0.001       | 0.742**  | 0.002 |

\* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

**10. Discussion**

The data presented here suggests that patients who previously treated with bladder preservation therapy and now came with recurrent or metastasis and patients who have distant metastasis at presentation and have renal impairment both groups of patients have improved PFS, OS and ORR when treated with single agent non-nephrotoxic gemcitabine with lower toxicity profile, although the efficacy results of our study was lower than that of combination regimens in previous studies.

In recurrent post-conservative therapy and in the metastatic setting, chemotherapy treatment remains the only therapeutic option. It has the objective to alleviate the symptoms, to improve the quality of life and to improve survival. In bladder TCC, chemotherapy showed very little progress and the standard (ddMVAC and GC) are still the most used regimens and that since several years. New drugs are in the process of development, including those used in targeted therapies for which the role remains to be defined more clearly. [10,11]

The specific chemotherapy regimen for advanced disease recommended partially depends on the presence or absence of medical co-morbidities, such as cardiac disease and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination chemotherapy alone has been reported only in good-risk patients, defined as those with good performance status, no visceral (ie, liver and lung) or bone disease, and normal alkaline phosphatase or lactate dehydrogenase levels. Poor-risk patients, defined as those with poor performance status or visceral disease, have consistently shown very poor tolerance to multi-agent combination programs and few complete remissions, which are prerequisites for the cure. [2]

Cisplatin, the taxanes, and gemcitabine are first-line chemotherapy options for advanced disease. GC and ddMVAC are commonly used in combinations that have shown clinical benefit, but GC remains the combination with the best ratio of efficacy/tolerability. [12]

A large, international, phase III study randomized 405 patients with locally advanced or metastatic disease to GC or standard MVAC. At a median follow-up of 19 months, overall survival and time to progression were similar in the two arms. Less toxic deaths were recorded among patients receiving GC compared to MVAC (1% vs. 3%), although this did not reach statistical significance. A 5-year update analysis confirmed that GC was not inferior to MVAC in terms of survival (overall survival, 13.0% vs. 15.3%; progression-free survival, 9.8% vs. 11.3%, respectively). [13,14]

Another large, randomized, phase III trial compared ddMVAC to standard MVAC. At a median follow-up of 7.3 years, 24.6% of patients were alive in the ddMVAC cohort compared with 13.2% in the standard MVAC cohort. There was one toxic death in each arm, but less overall toxicity was seen in the dose-dense group. From these data, standard MVAC is inferior to ddMVAC in terms of toxicity and efficacy, and is inferior to GC in terms of toxicity; therefore standard MVAC is no longer used. Both GC and ddMVAC with growth factor support are category 1 recommendations for metastatic disease. Alternative first-line regimens also include carboplatin or taxane-based regimens or single agent chemotherapy. [15]

The performance status of the patient is a major determinant in the selection of a regimen. Regimens with lower toxicity profiles are recommended in patients with compromised liver or renal status or serious comorbid conditions. In patients with a glomerular filtration rate (GFR) less than 60 mL/min, carboplatin may be substituted for cisplatin. A phase II/III study assessed 2 carboplatin-containing regimens in medically unfit patients (performance status 2). The overall response rate was 42% for gemcitabine plus carboplatin and 30% for methotrexate,
carboplatin, and vinblastine. However, the response rates dropped to 26% and 20%, respectively, with increased toxicity among patients who were both unfit and had a renal impairment (GFR <60 mL/min). [16]

Taxanes have been shown to be active as both front-line and palliative therapies. Based on these results, several groups are exploring 2- and 3-drug combinations using these agents, with and without cisplatin, as initial therapy. The alternative regimens, including cisplatin / paclitaxel, gemcitabine / paclitaxel, cisplatin / gemcitabine / paclitaxel, carboplatin / gemcitabine / paclitaxel, and cisplatin / gemcitabine / docetaxel, have shown modest activity in patients with bladder cancer in phase I-II trials. A randomized phase III trial was conducted to compare GC and GC plus paclitaxel in 626 patients with locally advanced or metastatic urothelial cancer. The addition of paclitaxel to GC resulted in higher response rates and a borderline overall survival advantage, which was not statistically significant in the intent-to-treat analysis. Analysis of eligible patients only (92%) resulted in a small (3.2 months) but statistically significant survival advantage in favor of the 3-drug regimen ($P = .03$). There was no difference in progression-free survival. The incidence of neutropenic fever was substantially higher with the 3-drug combination (13.2% vs. 4.3%; $P < .001$). Panelists feel that the risk of adding paclitaxel outweighs the limited benefit reported from the trial.[17-21]

Although current data are insufficient to recommend the above alternative regimens as routine first-line options, non-cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin because of renal impairment or other co-morbidities (category 2B). The NCCN Panel recommends enrollment in clinical trials of potentially less toxic therapies. [2]

Cisplatin, while it remains the most active drug in the treatment of bladder cancer, is associated with significant toxicities such as nausea and vomiting, myelosuppression, nephrotoxicity, neurotoxicity, ototoxicity as well as others. Since bladder cancer is a disease of older patients with co-morbidities including tobacco-associated lung disease, cardiac disease, a renal insufficiency as well as others that may preclude use of standard cisplatin-based combination chemotherapy making the treatment in elderly patients with renal impairment is challenging with the need for alternative non-platinum agent as well as the development of clinical trials investigating novel management strategies in this patient population.

We now have a new population of patients that have been recurrent after treatment in the front-line setting with bladder preservation and patients who have metastatic disease at presentation, both groups were elderly and have renal impairment. Thus we are faced with the question of how to treat these patients? Should patients treat with gemcitabine single agent chemotherapy which is not nephrotoxic? The goal of this study was to examine outcomes of patients with recurrent post-conservative therapy and in metastatic TCC of the urinary bladder. Specifically, we aimed to see PFS, OS & CBR in patients who were treated with single-agent gemcitabine.

Anti-tumor activity has been demonstrated with several single-agents among them is gemcitabine was shown and is still, the most highly promising single-agent activity in this disease, although these have rarely produced an improvement in survival when used alone. [22–32]

Gemcitabine was initially evaluated in an Italian phase I study conducted in 15 patients with metastatic bladder cancer. [33]

The doses ranged from 875 to 1.370 mg/m2. One complete response and 2 partial responses were seen in 14 previously treated patients and 1 partial response was observed in a chemotherapy-naive patient. The overall response rate was 27% (4.3–49.1%, 95% CI). [34]

In two phase II trials in previously treated patients, a response rate of 28% and 50% was reported. [35,36]

Two trials evaluating gemcitabine in previously untreated patients confirmed the high activity of this agent. Stadler et al. treated 40 patients with gemcitabine 1200 mg/m2 weekly times three, repeated every 28 days, and reported an overall response rate of 28% (15–45%, 95% CI). Three complete responses were obtained in patients with liver metastasis. [37]

Additionally, Moore et al. confirmed in 37 non-treated patients an overall response rate of 24.3% (12–41%, 95% CI). [38]

Gemcitabine, when used as a single agent, has minimal toxicity and may be a suitable alternative in non-cisplatin candidates. [39]

Gemcitabine has a favorable toxicity profile and is well tolerated in cisplatin-ineligible patients with moderately impaired renal function. It is a pyrimidine antimetabolite which inhibits cellular DNA synthesis and has single-agent activity against urothelial cancer in various clinical settings. [40]

11. Conclusions

Chemotherapy plays a major role in the management of bladder cancer. In the patients with recurrent disease, post-bladder preservation therapy and in patients with a metastatic setting at diagnosis, palliative chemotherapy based on cisplatin-type MVAC, dd-MVAC, or GC remains the treatment of choice. In unfit patients, Carboplatin-based chemotherapy type Gemcitabine-Carboplatin or Methotrexate-Carboplatin-Vinblastine (MCAVI) is a good option for these patients. In elderly patients with renal impairment single agent Gemcitabine is a valid option. Novel therapies, targeting angiogenesis, have been shown to be very promising. Therapeutic investigations should be continued with the development of new drugs and targeted therapies to improve treatment results in the metastatic bladder cancer. [41,42]
12. Abbreviations

CT: Computer tomography,
DDMVAC: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin,
GFR: Glomerular filtration rate,
G-CSF: Colony stimulating factor,
RECIST: Response evaluation criteria in solid tumors,
TCC: Transitional cell carcinoma,
TURBT: transurethral resection of the bladder tumor,
WHO-PS: World Health Organization Performance state.

REFERENCES

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559415.

[2] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer Version 1.2016.

[3] Wallerand H: Intravesical chemotherapy and bladder cancer. Prog Urol 2009, 19(12):868-71.

[4] Rathkopf D, Seher H: Multidisciplinary Management of Genitourinary Malignancies in Malcolm R. Alison, editor. The cancer handbook. 2 edition. London: Jon Wiley & Son; 2007, 1432-52.

[5] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. CA Cancer J Clin 2011, 61(2):69-90, Epub 2011 Feb 4.

[6] Boyle H, Fléchon A, Droz JP: Treatment of uncommon malignant tumours of the bladder. Curr Opin Urol 2011, 21(5):309-14.

[7] Ismaiel N, Arifi S, Flechon A, El Mesbah O, Blay JY, Droz JP, et al: Small cell cancer of the bladder: pathology, diagnosis, treatment and prognosis. Bull Cancer 2009, 96(6): E30-44.

[8] Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J 2009; 3: S193-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20019984.

[9] Kirkali, Z., Chan, T., Manoharan, M., Algaba, F., Busch, C., Cheng, L. et al. (2005) Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 66(6 Suppl. 1): 4_34.

[10] Wu, X.R. (2005) Urothelial tumorigenesis: a tale of divergent pathways. Nat Rev Cancer 5: 713-725.

[11] Boyle H, Fléchon A, Droz JP: Treatment of uncommon malignant tumours of the bladder. Curr Opin Urol 2011, 21(5):309-14.

[12] Bellmunt J, der MH V, Mead GM, Skoneczna I, De SM, Daugaard G, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012; 30: 1107-13.

[13] der MH V, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with bladder cancer. J Clin Oncol. 2005; 23: 4602-8.

[14] von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000; 18: 3068- 3077. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11001674.

[15] Sternberg CN, De MP, Schornagel JH, Theodore C, Fossa SD, van Oostrom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer. 2006; 42: 50-4.

[16] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II–results of EORTC study 30986. J Clin Oncol 2009; 27:5634-5639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19786668.

[17] Burch PA, Richardson RL, Cha SS, et al. Phase II study of paclitaxel and cisplatin for advanced urothelial cancer. J Urol 2000; 164: 1538-1542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11025699.

[18] Meluch AA, Greco FA, Burris HA, 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol 2001; 19: 3018-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11408496.

[19] Bellmunt J, Guillem V, Paz-Ares L, et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol 2000; 18: 3247-3255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10986057.

[20] Hussain M, Vaishampayan U, Du W, et al. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 2001; 19: 2527-2533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11331332.

[21] Pectasides D, Glotsos J, Bountouroglou N, et al. Weekly chemotherapy with docetaxel, gemcitabine and cisplatin in advanced transitional cell urothelial cancer: a phase II trial. Ann Oncol 2002; 13:243-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11886001.

[22] Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012; 30: 1107-13.

[23] M. J. Moore, E. Winquist, E. E. Vokes et al. Phase II study of oxaliplatin in patients with inoperable, locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCC) who have received prior chemotherapy. Proc Am Soc
Gemcitabine Single Agent for Recurrent Post Bladder Preservation Therapy and in Metastatic Transitional Cell Carcinoma of Urinary Bladder in Elderly Patients with Renal Impairment

Clin Oncol 2003; 22: 408 (abstr 1638).

[24] Culinie S, Rebillard X, Iborra F et al. Gemcitabine and oxaliplatin in advanced transitional cell carcinoma of the urothelium: a pilot study. Anticancer Res 2003; 23: 1903–6.

[25] Font A, Esteban E, Carles J et al. Gemcitabine and oxaliplatin combination: A multicenter phase II trial in unfit patients with locally advanced or metastatic urothelial cancer. Proc Am Soc Clin Oncol 2004; 23: 391 (Abstract 4544).

[26] Khorsand M, Lange J, Feun L et al. Phase II trial of oral piritrexim in advanced, previously treated transitional cell cancer of bladder. Invest New Drugs 1997; 15: 157–163.

[27] Sternberg CN. Gemcitabine in Bladder Cancer. Semin Oncol 2000; 27: 31–9.

[28] von der Maase H. Gemcitabine in transitional cell carcinoma of the urothelium. Expert Rev Anticancer Ther 2003; 21: 11–9.

[29] Misset JL. Brief communication: use of the multitargeted antifolate pemetrexed (Alimta) in genitourinary cancer. Semin Oncol. 2002; 29 (1 Suppl 3): 36–9.

[30] Sternberg, CN, Vogelzang, NJ. Gemcitabine, Paclitaxel, Pemetrexed and Other Newer Agents in Urothelial and Kidney Cancers. Crit Rev Oncol Hematol. 2003; 46 (Suppl: S10) 5–15.

[31] Bellmunt J, Albiol S. New chemotherapy combinations for advanced bladder cancer. Curr Opin Urol. 2001; 11: 517–22.

[32] Calabro F, Sternberg CN. High-risk metastatic urothelial cancer: chances for cure? Curr Opin Urol 2002; 12(5): 441–8.

[33] Calabro F, Sternberg CN. New drugs and new approaches for the treatment of metastatic urothelial cancer. World J Urol 2002; 20: 158–66.

[34] Pollera CF, Ceribelli A, Grecco M et al. Weekly gemcitabine in advanced bladder cancer. A preliminary report from a phase I study. Ann Oncol 1994; 5: 182–184.

[35] Lorusso V, Pollera CF, Antimi M et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer 1998; 34: 1208–1212.

[36] Albers P, Siener R, Perabo F et al. Gemcitabine Monotherapy as 2nd-Line Treatment in Cisplatin Refractory Transitional Cell Carcinoma. Proc Am Soc Clin Oncol 2000; Abstr 1360.

[37] Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA: Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. J Clin Oncol 1997; 15: 3394–3398.

[38] Moore MJ, Tannock I, Ernst S, Huan S, Murray N: Gemcitabine: A promising new agent in the treatment of advanced urothelial cancer. J Clin Oncol 1997; 15: 3441–3445.

[39] Lichtman, S.M. and Boparai, M.K. (2008) Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. Curr Treat Options Oncol 9: 191_203.

[40] De Santis M, Bellmunt J, Mead G et al. Randomized phase II/III trial assessing gemcitabine / carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin based chemotherapy: EORTC study 30986. J Clin Oncol 2012; 30(2): 191–199.

[41] Ismaili N, Amzerin M, Elmaajouli S, Droz JP, Flechon A, Errihani H: The role of chemotherapy in the management of bladder cancer. Prog Urol 2011, 21(6):369-82.

[42] Ismaili N, Elmaajouli S, Bensouda Y, Belbaraka R, Abahssain H, Allam W, et al: Neoadjuvant or adjuvant chemotherapy: what is the best treatment of muscle invasive bladder cancer? Oncol Rev 2011.