Survival Rate of Gemcitabine Monotherapy after Prior Platinum-based Chemotherapy for Metastatic Bladder Cancer

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ABSTRACT

Background: Bladder cancer is the most common type of cancer in the urinary system and the eleventh most common cancer in the world. The overall 5-year survival of bladder cancer in metastatic stage is very low. The standard first-line chemotherapy for bladder cancer is M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) and GC (gemcitabine, cisplatin) while the second-line is vinflunine. Gemcitabine has shown a higher response rate than vinflunine as a second-line treatment. But, the overall survival-rate of gemcitabine is still unknown. **Objective:** To determine whether gemcitabine monotherapy can increase the survival rate in metastatic bladder carcinoma after prior platinum-based chemotherapy. **Methods:** A literature search was through 3 databases: Pubmed, Scopus, and Cochrane. Studies were selected based on PICO and eligibility criteria for this report. Four studies from 3 databases were selected and critically appraised using Oxford University's Center of Evidence-Based Medicine (CEBM) form. **Result:** Gemcitabine monotherapy may increase the survival rate of metastatic bladder cancer patients. However, gemcitabine has several severe side effects and the validity of the studies is low. **Conclusion:** Gemcitabine monotherapy may increase the survival rate of metastatic bladder cancer patients, but the evidence level is low.

Keywords: Bladder cancer, gemcitabine monotherapy, survival rate

ABSTRAK

Latar belakang: Kanker kandung kemih merupakan kanker sistem saluran kemih yang paling umum dan merupakan kanker paling umum kesebelas di dunia. Kesintasan 5 tahun kanker kandung kemih cukup tinggi, namun sangat rendah pada kondisi metastasis. Kemoterapi standar lini pertama untuk kanker kandung kemih adalah M-VAC (*methotrexate, vinblastine, doxorubicin, cisplatin*) dan GC (*gemcitabine, cisplatin*), sedangkan lini kedua adalah *vinflunine*. *Gemcitabine* sebagai pengobatan lini kedua telah menunjukkan tingkat respons lebih tinggi daripada *vinflunine*. Namun, kesintasan monoterapi *gemcitabine* sebagai terapi lini kedua setelah kemoterapi berbasis *platinum* secara keseluruhan masih belum diketahui. **Tujuan:** Mengetahui apakah monoterapi *gemcitabine* sebagai terapi lini kedua setelah kemoterapi berbasis *platinum* dapat meningkatkan tingkat kelangsungan hidup pasien kanker kandung kemih yang metastatik. **Metode:** Pencarian literatur menggunakan 3 *database,* yaitu Pubmed, Scopus, dan Cochrane. Studi dipilih berdasarkan PICO dan kriteria kelayakan yang sesuai untuk laporan ini. Empat studi terpilih dinilai secara kritis menggunakan formulir *center of evidence based medicine* dari Universitas Oxford. **Hasil:** Monoterapi *gemcitabine* dapat meningkatkan angka kelangsungan hidup pasien kanker kandung kemih yang mengalami metastasis. Namun, *gemcitabine* memiliki beberapa efek samping berat dan validitas penelitian rendah. **Simpulan:** Monoterapi *gemcitabine* dapat meningkatkan tingkat kelangsungan hidup pada pasien kanker kandung kemih metastatik, namun *level of evidence* rendah. **Yusuf Mushlih, Kemal Akbar Suryoadji, Findy Prasetyawaty. Kesintasan Pasien Kanker Kandung Kemih dengan Metastatis pada Monoterapi *Gemcitabine* setelah Kemoterapi Berbasis Platinum**

Kata kunci: Kanker kandung kemih, monoterapi *gemcitabine*, tingkat kelangsungan hidup

Introduction

Bladder cancer is the most common type of cancer in the urinary system. Among several types of bladder cancer, the most common is urothelial carcinoma (approximately 90% cases). Other types include squamous cell carcinoma, adenocarcinoma small cell carcinoma, and sarcoma. In 2020, bladder cancer was the eleventh most common cancer in the world. There were 573.278 new cases in 2020, representing 3% of all new cancer cases and there were 212.536 deaths, representing 2.1% of all cancer deaths.[1–3] Risk factors for bladder cancer include male gender, age over 65, genetic factors, alcohol, exposure to carcinogens, and obesity.[2] Bladder cancer can spread and invade the urethra, prostate, uterus, and vagina; metastasis is through the lymphatic system and the circulatory system. Lymphagenous metastasis usually spread to the presacral, obturator, iliac, and para-aortic lymph node. Hematogenous metastasis usually spread to the liver, bones, lungs, and adrenal glands.[2]

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Survival of bladder cancer is greatly affected by its stage and treatment. The 5-year survival rate is 77.1% for bladder cancer in all stages, 95.8% for early diagnosed bladder cancer, 69.5% for localized bladder cancer, 36.3% for regional disease, and 4.6% for metastatic disease.[2] The survival rate after radical cystectomy is significantly higher than with transurethral resection of the urinary bladder tumor (TURBT).[2] Another study also found that multimodality treatment has a 52% 5-year survival rate, similar to cystectomy in the same patient group.[4]

The standard first-line chemotherapy for metastatic bladder cancer is M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) and GC (gemcitabine and cisplatin).[5] The use of M-VAC and GC had associated with increased survival. Recently GC is becoming the standard first-line therapy due to its lower toxicity compared to M-VAC.[5] Besides M-VAC does not offer a very good prognosis.[6] Vinflunine is the standard second-line chemotherapy for metastatic bladder cancer because it has the highest level of evidence reported to date with an overall response rate of 8.6%.[5] Gemcitabine second-line monotherapy is reported to have a high response rate around 25-29%, higher than vinflunine.[7]

This Evidence-Based Case Report analyzes the survival rate of metastatic bladder cancer patient who received gemcitabine monotherapy after platinum-based chemotherapy.

Case Illustration

A 56 year-old patient came with blood in urine, pain while urinating, weak urine stream, and high urinary frequency (15 times a day) in March 2019. In 2007, the patient experienced similar symptoms and was diagnosed with low-grade TCC (transitional cell carcinoma) after USG and biopsy findings. The patient underwent transurethral resection of the urinary bladder tumor (TURBT) and radiation treatment until September 2018. The patient was diagnosed with bladder TCC T4N1M1 with lung metastasis. The patient underwent nephrostomy, 6 cycles of gemcitabine + carboplatin and 6 cycles of carboplatin + paclitaxel, and 2 out of 6 cycles of M-VAC. The patient was infected by COVID-19 in January 2021. The patient was scheduled to undergo bilateral nephrostomy in March 2021 but delayed due to the positive PCR COVID-19 test. M-VAC treatment is also delayed due to COVID-19. Now, the patient has recovered from COVID-19.

Clinical Question

How is the survival rate of gemcitabine monotherapy in metastatic bladder cancer after platinum-based chemotherapy?

METHODS

Search Strategy

Literature searching was done on 27 February 2021 using PubMed, Scopus, and Cochrane. Keywords used in this literature search are "survival" AND "gemcitabine" AND "monotherapy" AND "urothelial cancer". Searches were limited to trials, case-control, cohort, systematic review, or meta-analysis. The selection strategy can be seen in **Table 1**.

Table 1. PICO formulation

Patient/Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Advanced or metastatic urothelial cancer after platinum-based chemotherapy	Gemcitabine monotherapy	No gemcitabine/ best supportive care	Survival rate
Type of Questions	Intervention		
Study Design	Randomized controlled trial, systematic review, meta-analysis, case-control, cohort		

Table 2. Literature search strategy

Database	Search Strategy	Hits
PubMed	("bladder cancer"[Title/Abstract] OR "bladder carcinoma"[Title/Abstract] OR "urinary bladder neoplasm*"[Title/Abstract] OR "urothelial cancer"[Title/Abstract] OR "transitional cell carcinoma"[Title/Abstract]) AND ("metasta*"[Title/Abstract] OR "stage iv"[Title/Abstract] OR "stage 4"[Title/Abstract] OR "severe"[Title/Abstract] OR "advance*"[Title/Abstract]) AND ("gemcitabine"[Title/Abstract] AND ("monotherapy"[Title/Abstract] OR "monotreatment"[Title/Abstract] OR "single-therapy"[Title/Abstract] OR "single therapy"[Title/Abstract])) AND ("platin*"[Title/Abstract] OR "platinum based"[Title/Abstract] OR "platinum-based"[Title/Abstract] OR "platinum"[Title/Abstract] OR "cisplatin*"[Title/Abstract] OR "oxaliplatin*"[Title/Abstract] OR "carboplatin*"[Title/Abstract]) AND "surviv*"[Title/Abstract]	20
Scopus	("bladder cancer" OR "bladder carcinoma" OR "urinary bladder neoplasm*" OR "urothelial carcinoma" OR "transitional cell carcinoma") AND ("metasta*" OR "stage iv" OR "stage 4" OR "severe" OR "advance*") AND ("gemcitabine" AND ("monotherapy" OR "monotreatment" OR "single-therapy" OR "single therapy")) AND ("platin*" OR "platinum based" OR "platinum-based" OR "platinum" OR "cisplatin*" OR "oxaliplatin*" OR "carboplatin*") AND "surviv*"	171
Cochrane	#1 MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees #2 metasta* OR "stage iv" OR "stage 4" OR severe OR advance* #3 #1 AND #2 #4 gemcitabine #5 monotherapy OR monotreatment OR "single therapy" OR "single-therapy" #6 #4 AND #5 #7 platin* OR "platinum based" OR "platinum-based" OR platinum OR cisplatin* OR oxaliplatin* OR carboplatin* #8 surviv* #9 #3 AND #6 AND #7 AND #8	3

Eligibility Criteria

The inclusion criteria:

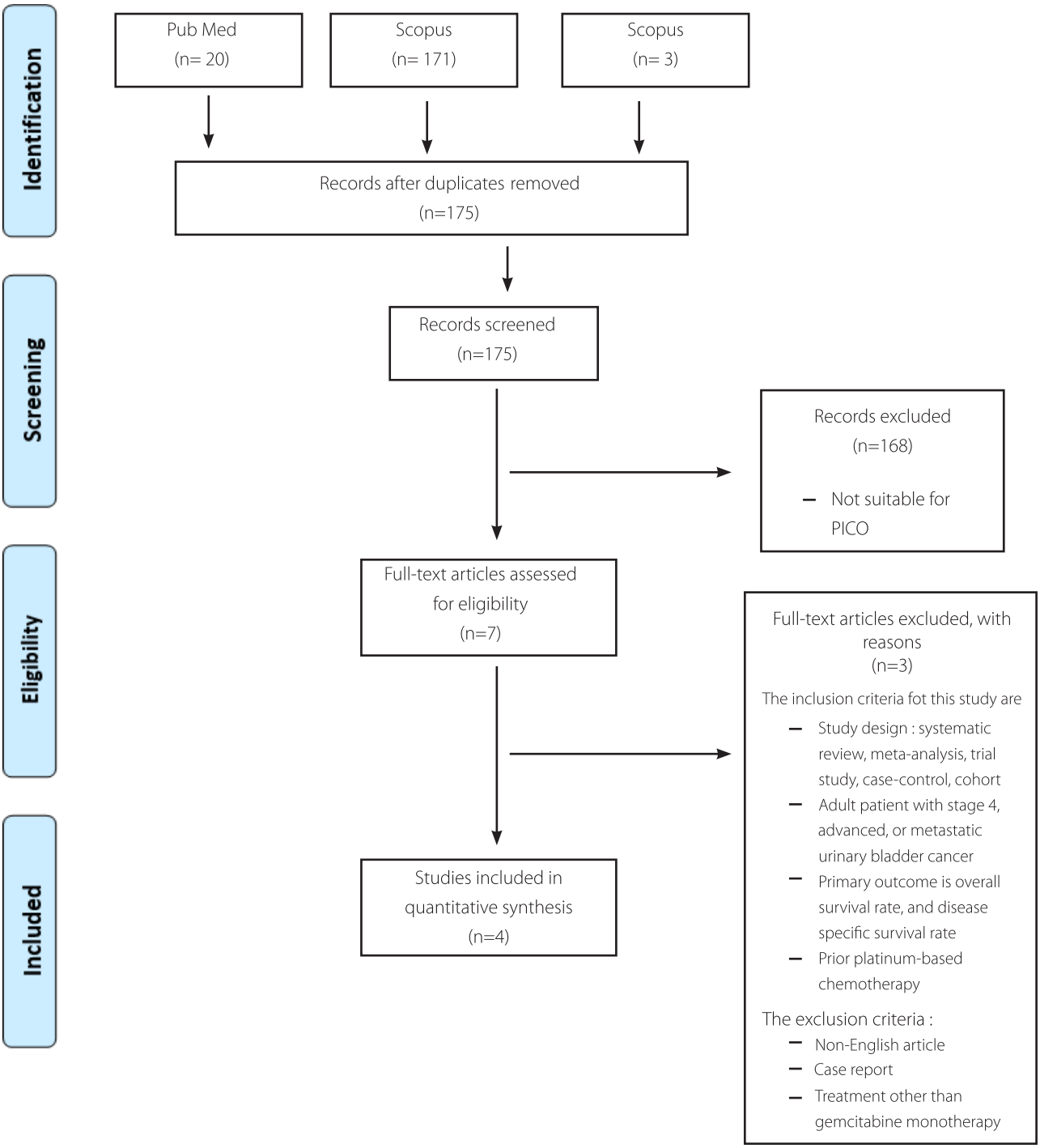
- Study design: systematic review, meta-analysis, trial study, case-control, cohort
- Adult patient with stage 4, advanced, or metastatic urinary bladder cancer
- Primary outcome is overall survival rate, and disease-specific survival rate

Prior platinum-based Chemotherapy The exclusion criteria:

- Non-English article
- Case report
- Treatment other than gemcitabine monotherapy

Article Selection

A total of 194 studies were retrieved from three databases. After screening and excluding the studies based on PICO and inclusion and exclusion criteria, 4 studies were chosen for critical appraisal.



Picture 1. Searching strategy.

RESULTS

Study Characteristic

Two trials, one case-control, and one prospective cohort study are included in this report. Those 4 studies are written by Akaza H, *et al*, (2007),[8] Soga N, *et al*, (2010),[9] Muto S, *et al*, (2015),[10] Kalogirou C, *et al*, (2016).[11] Each of study characteristics is summarized in table 3.

Table 3. Study characteristics

Questions	Akaza H (2007)	Soga N (2010)	Muto S (2015)
Was the assignment of patients to treatment randomized?	No, there was no control group, only the intervention group in this study. The patient was only assigned to the intervention group.	No, there was no control group, only the intervention group in this study. The patient was only assigned to the intervention group.	No, the patient was only assigned to the intervention group. This study used retrospective patient data for the control group.
Were all the patients who entered the trial accounted for its conclusion ? And were they analyzed in the groups to which they were randomized?	No, 2 patients were excluded; one did not meet the study criteria and the other suddenly worsened before the first administration of the study drug.	Yes, all patients completed follow up	Yes, all patients completed follow up
Were patients and clinicians kept blind to treatment ?	No, the patients and researchers were not blinded because there was only 1 study group	No, the patients and researchers were not blinded because there was only 1 study group	No, the patients and researchers were not blinded because the patients were only assigned to the intervention group. The control group used retrospective patient data
Aside from the experimental treatment, were the groups treated equally?	Yes, no other chemotherapy, immunotherapy, hormonal cancer therapy, or experimental medications were allowed while the patient was on this study.	Yes, no other chemotherapy, immunotherapy, hormonal cancer therapy, or experimental medications were allowed while the patient was on this study.	Yes, the intervention group received gemcitabine monotherapy while the retrospective control group only received best supportive care
Were the groups similar at the start of the trial	Yes, patients were eligible for enrollment if they were 20 to 74 years of age, had a histologically or cytologically confirmed TCC of the urothelium with advanced or metastatic disease, a recurrence or progression following treatment with a first-line platinum-based regimen, An ECOG performance status of 0–2, and an estimated life expectancy of at least 3 months	Yes, patients were eligible for enrollment if they had proven histological diagnosis of urothelial carcinoma (UC) with a measurable metastatic site following first-line M-VAC therapy and second-line paclitaxel/carboplatin (Pca) therapy	Yes, All patients were included if they had confirmed metastatic UC following first, second, or third-line platinum-based chemotherapy.

Author (Year)	Study Design	Population	Intervention	Comparison	Outcome	Gemcitabine monotherapy	Control/best supportive care
Akaza H (2007)	Multicenter, open-label, phase II study	44 Patient with advanced or metastatic transitional cell carcinoma (TCC) disease after first-line platinum-based chemotherapy.	44 patients received gemcitabine monotherapy on days 1, 8, and 15 of a 28 day cycle	0 control group patient	1-year overall survival rate	52.3%	-
Soga N (2010)	Prospective cohort study	13 patients with metastatic urothelial cancer after first and second-line platinum-based chemotherapy	38 patients received gemcitabine monotherapy on days 1, 8, and 15 of a 28 day cycle	0 control group patient	1-year overall survival rate	30.8%	
					2-year overall survival rate	15.3%	

Muto S (2015)	Non-randomized controlled trial	66 patients with metastatic urothelial cancer after first, second, or third-line platinum-based chemotherapy	33 patients received gemcitabine maintenance monotherapy every 4 weeks	33 retrospective control group patient	1-year disease-specific survival rate	61%	11.2%
					2-year disease-specific survival rate	45.4%	11.2%
Kalogirou C (2016)	Case-control	76 patients with surgically treated advanced urothelial cancer prior to primary cisplatin-based chemotherapy	38 patients received gemcitabine maintenance monotherapy on days 1 and 8 of a 28 day cycle	38 retrospective control collective group patient	5-year overall survival rate	49.2%	26.5%
					5-year cancer specific survival rate	61.3%	33.4%

Critical Appraisal

Critical appraisal was carried out by assessing the study's validity, importance, and applicability. The 4 studies presented in this paper were appraised using tools from Center Of Evidence Based Medicine Oxford University (CEBM).[12] One of the study was appraised using the case-control tools/form while the other 3 studies was appraised using the RCT (randomized controlled trial) tools/form.

Validity for RCT

Table 4. Validity of Akaza H (2007),[8] Soga N (2010),[9] and Muto S (2015).[10]

Questions	Akaza H (2007)	Soga N (2010)	Muto S (2015)
Was the assignment of patients to treatment randomized?	No, there was no control group, only the intervention group in this study. The patient was only assigned to the intervention group.	No, there was no control group, only the intervention group in this study. The patient was only assigned to the intervention group.	No, the patient was only assigned to the intervention group. This study used retrospective patient data for the control group.
Were all the patients who entered the trial accounted for its conclusion ? And were they analyzed in the groups to which they were randomized?	No, 2 patients were excluded; one did not meet the study criteria and the other suddenly worsened before the first administration of the study drug.	Yes, all patients completed follow up	Yes, all patients completed follow up
Were patients and clinicians kept blind to treatment ?	No, the patients and researchers were not blinded because there was only 1 study group	No, the patients and researchers were not blinded because there was only 1 study group	No, the patients and researchers were not blinded because the patients were only assigned to the intervention group. The control group used retrospective patient data
Aside from the experimental treatment, were the groups treated equally?	Yes, no other chemotherapy, immunotherapy, hormonal cancer therapy, or experimental medications were allowed while the patient was on this study.	Yes, no other chemotherapy, immunotherapy, hormonal cancer therapy, or experimental medications were allowed while the patient was on this study.	Yes, the intervention group received gemcitabine monotherapy while the retrospective control group only received best supportive care
Were the groups similar at the start of the trial	Yes, patients were eligible for enrollment if they were 20 to 74 years of age, had a histologically or cytologically confirmed TCC of the urothelium with advanced or metastatic disease, a recurrence or progression following treatment with a first-line platinum-based regimen, An ECOG performance status of 0–2, and an estimated life expectancy of at least 3 months	Yes, patients were eligible for enrollment if they had proven histological diagnosis of urothelial carcinoma (UC) with a measurable metastatic site following first-line M-VAC therapy and second-line paclitaxel/carboplatin (Pca) therapy	Yes, All patients were included if they had confirmed metastatic UC following first, second, or third-line platinum-based chemotherapy.

Validity for Case-Control

Table 5. Validity of Kalogirou C (2016)[11]

Questions	Kalogirou C (2016)
Did the study address a clearly focused question / issue?	Yes. The focus of this study was to find the 5-year overall survival (OS), cancer-specific survival (CSS), and progression-free (PFS) survival of gemcitabine maintenance monotherapy in advanced urothelial carcinoma patient who had received cisplatin-based combination chemotherapy.
Is the research method (study design) appropriate for answering the research question?	No, the appropriate study design for therapy study is RCT
Were there enough subjects (employees, teams, divisions, organizations) in the study to establish that the findings did not occur by chance?	Can't tell. There were 38 patients in the case and control group but it wasn't mentioned why they only use 38 subjects.
Was the selection of cases and controls based on external, objective, and validated criteria?	No. Cases included in this study were patients with "advanced urothelial carcinoma" but the study never exactly defined what is an "advanced urothelial carcinoma" was.
Were both groups comparable at the start of the study?	Yes. The control group was matched by propensity score matching, using the bioconductor package 'MatchIt' for R, version 3.10.
Were objective and unbiased outcome criteria used?	Can't tell. The objectives of this study were to determine the OS, CSS, and PFS rates using Kaplan-Meier estimates. But the criteria for OS, CSS, and PFS were not mentioned.
Is there data-dredging?	Can't tell
Are objective and validated measurement methods used to measure the outcome? If not, was the outcome assessed by someone who was unaware of the group assignment (i.e. was the assessor blinded)?	Can't tell. The objectives of this study were to determine the OS, CSS, and PFS rates using Kaplan-Meier estimates. But the criteria for OS, CSS, and PFS were not mentioned. The assessor was not blinded in this study
Is the size effect practically relevant?	Yes. The effect is relevant for our patient
How precise is the estimate of the effect? Were confidence intervals given?	No, there were no confidence intervals in this study
Could there be confounding factors that haven't been accounted for?	No
Can the results be applied to your organization?	Yes, it can be applied to our organization.

Importance

Table 6. Importance of Akaza H(2007)[9] and Soga N(2010).[10]

	Akaza H (2007)					Soga N (2010)				
Outcomes	Gemcitabine monotherapy group % (95% CI)	Control group % (95% CI)	Relative Benefit Increase	Absolute Benefit Increase	Number Needed To Treat	Gemcitabine monotherapy group % (95% CI)	Control group % (95% CI)	Relative Benefit Increase	Absolute Benefit Increase	Number Needed To Treat
1-year overall survival rate	53%	-	-	-	-	30.8%	-	-	-	-
2-year overall survival rate	-	-	-	-	-	15.3%	-	-	-	-
5-year overall survival rate	-	-	-	-	-	-	-	-	-	-
1-year disease specific survival rate	-	-	-	-	-	-				
2-year disease specific survival rate	-	-	-	-	-	-				
5-year disease specific survival rate	-	-	-	-	-	-	-	-	-	-

Table 7. Importance of Muto S (2015)[11] and Kalogirou C(2016).[12]

	Muto S (2015)					Kalogirou C (2016)				
Outcomes	Gemcitabine maintenance monotherapy group % (95% CI)	Control group % (95% CI)	Relative Benefit Increase	Absolute Benefit Increase	Number Needed To Treat	Gemcitabine monotherapy group % (95% CI)	Control group % (95% CI)	Relative Benefit Increase	Absolute Benefit Increase	Number Needed To Treat
1-year overall survival rate	-	-	-	-	-	-	-	-	-	-
2-year overall survival rate	-	-	-	-	-	-	-	-	-	-
5-year overall survival rate	-	-	-	-	-	49.2%	26.5%	85.6%	22.7%	4.4
1-year disease specific survival rate	61% (43.5-78.5)	11.2% (0-24.8)	444.6%	49.8%	2	-	-	-	-	-
2-year disease specific survival rate	45.4% (26.9-64)	11.2% (0-24.8)	305.3%	34.2%	2.9	-	-	-	-	-
5-year disease-specific survival rate	-	-	-	-	-	61.3%	33.4%	83.5%	27.9%	3.5

Applicability

Tabel 8. Applicability of the studies.

Questions	Akaza H (2007)	Muto S (2015)	Kalogirou C (2016)	Soga N (2010)
Do these results apply to your patient?	Yes, because the study subjects were adult patients with histologically or cytologically confirmed TCC of the urothelium with advanced or metastatic disease and had been administered platinum-based chemotherapy	Yes, because the study subjects were adult patients with confirmed metastatic UC and had been administered standard platinum-based chemotherapy	Yes, because the study subjects were adult patients with confirmed advanced UC after primary cisplatin-based chemotherapy.	Yes, because the study subjects were adult patients with proven histological diagnosis of UC with a measurable metastatic site following platinum-based chemotherapy.
How great would the potential benefit of therapy be for your patient?	Yes, although this study didn't use a control group, it showed that gemcitabine's overall response rate was higher than other monotherapy drugs based on comparative studies.	Yes, gemcitabine maintenance monotherapy was significantly better than best supportive care alone in increasing 1 and 2-year disease-specific survival rate among metastatic UC patients following platinum-based chemotherapy	Yes, gemcitabine maintenance monotherapy was significantly better than best supportive care alone in increasing 5-year overall and cancer-specific survival rate among advanced UC patients following primary platinum-based chemotherapy	No, because the study didn't have a control group so it couldn't be concluded if gemcitabine monotherapy was better than best supportive care alone
Do your patient's values and preferences satisfied by the regimen and its consequences?	Yes, because gemcitabine monotherapy can be the therapy of choice for metastatic UC after platinum-based chemotherapy to increase patient's survival and decrease severe adverse events.	Yes, because gemcitabine monotherapy can be the therapy of choice for metastatic UC after platinum-based chemotherapy to increase patient's survival and has fewer side effects than standard platinum-based chemotherapy.	Yes, because gemcitabine monotherapy can be the therapy of choice for metastatic UC after platinum-based chemotherapy to increase patient's survival and has low adverse effects	Yes, because gemcitabine monotherapy can be the therapy of choice for metastatic UC after platinum-based chemotherapy to increase patient's survival

DISCUSSION

Bladder cancer, also known as urothelial carcinoma (UC) or transitional cell carcinoma (TCC), is a type of cancer from the urinary tract, from the renal pelvis, ureter, bladder, to the proximal two-thirds of the urethra. Most of UC occurs in bladder (90%), followed by renal pelvis (8%), ureter, and urethra (2%). Clinically, UC is divided into superficial (75%), muscle-invasive (20%), and metastatic (5%). UC also uses TNM staging for classification. Ninety five percent of urothelial carcinoma come from

the transitional cell, 3% are squamous cell origin, and 2% are adenocarcinoma.[2,13]

The pathogenesis of UC is still largely unknown. Many contributing factors are genetic alteration, UTI, smoking, schistosomiasis, extended use of catheter, occupational risk factors, and other risk factors.[13,14] The main pathogenesis is thought to be divided into two major categories, non-invasive papillary pathway and invasive pathway. The non-invasive papillary pathway originates from the stem cell of epithelial of the urothelium. These cells can proliferate and replace the existing epithelial layer every 6-12 months. Mutation and alteration of proto-oncogenes, such as FGFR-3, HRAS, PI3K, and tyrosine kinase receptor, can increase the risk of cancer originating from the stem cells. FGFR-3 mutations are found in 75% while HRAS mutations are found in 30% of the case of papillary tumors. Non-invasive tumors are associated with a good prognosis but have a high recurrence rate.[14,15] Invasive pathway, on the other hand, is mainly caused by alteration of tumor suppressor genes such as TP53, RB1, and PTEN. The invasive pathway can cause invasive bladder cancer that has a poorer prognosis compared to non-invasive type.[13-15]

Gemcitabine had been used to treat cancer for more than 15 years. Gemcitabine is a nucleoside analog; its anticancer mechanism is mainly to inhibit DNA synthesis. Gemcitabine can bind to DNA and prevent DNA polymerase to synthesize new DNA strands. This process leads to 'masked chain termination'. Gemcitabine can also induce apoptosis by activating p38 mitogen-activated protein kinase. The major side effect of gemcitabine is myelosuppression and it's the main reason for dose limitation. Myelosuppression can manifest as thrombocytopenia, neutropenia, or anemia. Other side effects can manifest as headache, myalgia, flu-like symptoms, arthralgia, malaise, rhinitis, and cough.[16,17]

Patients eligible in this study were adult, aged 18 or more with advanced or metastatic urothelial carcinoma who had received some kind of platinum-based chemotherapy. This study intervention was gemcitabine monotherapy and the outcome was survival rate.

Akaza, *et al*,[8] found that the 1-year survival rate of gemcitabine monotherapy was 52.3% with median time of survival for pelvis-ureter and bladder were 13.1 months and 11.5 months respectively. These results were lower in Soga, *et al*,[9] which the overall 1-year and 2-year survival rate after given gemcitabine monotherapy was 30.8% and 15.3% with a median time of survival of 7.3 months. This study also found that responders to the chemotherapy had a higher 1-year survival rate compared to non-responders with 75.1% and 12.5% respectively. However, both studies didn't have any control group to compare the result so the validity of these studies was low.[8,9]

Muto, *et al*, found that the 1- and 2-year disease-specific survival (DSS) for gemcitabine monotherapy was 61.0% (95% CI 43.5–78.5%) and 45.4% (95% CI 26.9–64.0%) respectively. The data showed a favorable significant survival rate compared to the control group with 1- and 2- year DSS of 11.2% (95% CI 0–24.8%). The median time to progression was also longer in the gemcitabine group with 12 months compared to 2 months in the control group. These results were somewhat similar to Kalogirou, *et al*, that recorded a higher 5-year overall (OS) and cancer-specific survival (CSS) rate in the gemcitabine monotherapy group compared to control. The 5-year OS and CSS rate for the gemcitabine group is 49.2% and 61.3% compared to 26.5% and 33.4% in the control group. Both studies showed promising survival outcomes for gemcitabine monotherapy compared to control. However, these studies didn't have high validity. Muto, *et al,* study was not randomized and used retrospective patient data as control while Kalogirou, et al was a case-control study. Study by Kalogirou, *et al*, also have a somewhat low validity for a case-control study.[10,11]

The response rate of gemcitabine monotherapy varied between these studies. Akaza, *et al*, reported a fairly high overall response rate of 25% while Soga, *et al*, reported only 7.7%. Other studies also reported varied response rates ranging from 11% to 29%. These results might be caused by differences in patient characteristics, environment, or gemcitabine dose.[7-9]

Gemcitabine monotherapy can also cause toxicities. Akaza, *et al,* reported that the most common toxicities were neutropenia at 86.4% with severe grade 3 or 4 toxicities in 50% patients. Other severe toxicities like leukopenia, anemia, and anorexia were present but not too frequent. Soga, *et al*, also reported that hematology alteration was the most common toxicities. Anemia, neutropenia, and thrombocytopenia were all found in 31% patients who received gemcitabine monotherapy. Muto, *et al*, found that grade 3 or more toxicities were found in 30.3% patients and 27.3% of them are hematological toxicities. Neutropenia was experienced by 9.1% patients; thrombocytopenia was experienced by 3%, and anemia by 12.1% patients. Kalogirou, *et al,* reported 7,8% patients who received gemcitabine monotherapy experienced adverse events but those events were not specified. These studies showed that hematology toxicities were the most common toxicities in gemcitabine chemotherapy and there were several severe adverse events reported in gemcitabine patients. However, gemcitabine monotherapy generally has lower and less serious adverse events than platinum-based chemotherapy.[8-11]

In conclusion, gemcitabine monotherapy after platinum-based chemotherapy may increase the survival rate in metastatic bladder cancer patients. However, gemcitabine monotherapy has several adverse effects that should be accounted for. These studies also have slightly different results on the survival rate of gemcitabine monotherapy even though all reported positive results. These results might be caused by differences in patient characteristics, environment, or gemcitabine dose. These studies also have a low level of validity because none is a randomized controlled trial.

Limitations of the studies are the small sample size, study design, and difference in gemcitabine dose and supportive care.

CONCLUSION

Gemcitabine monotherapy after platinum-based chemotherapy may increase the survival rate of metastatic bladder cancer patients. However, gemcitabine has several severe side effects that may outweigh the benefit of treatment. The validity of the studies regarding gemcitabine monotherapy is low because none are randomized controlled trial.

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