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Original Article

Five-year overall survival of patients with advanced bladder cancer in Kazakhstan: OSURK registry study

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Abstract: Background: The goals of the OSURK registry study were to assess 5-year overall survival (OS) in patients with metastatic urothelial cancer diagnosed in 2017 in Kazakhstan and collect data on the use of various treatment options in routine clinical practice. Methods: Patients with newly diagnosed metastatic bladder cancer (BC) were retrospectively identified in the national register of Kazakhstan (ERCP) between January 2017 and January 2018. ERCP is the biggest register in the country and includes patient data from 17 regions. Investigators collected patient information and processed records online on the following anonymised data: demographical characteristics, received treatment and outcomes. Patients were included in the study if mBC was confirmed histologically and they had at least one visit to the cancer center during the follow-up period. The outcomes of interest were overall survival (OS), patient characteristics and treatment patterns. Results: Totally 480 adult patients with metastatic BC were included. Mean number of patients in one region per year was 28.2. Median age at diagnosis of mBC was 70.0 years (range, 30-100). Patients were predominantly male (81.3%), histological subtype of BC (urothelial carcinoma, etc.) was determined in 41%. Overall, 187 (39%) patients received systemic therapy for metastatic disease. Platinum-based chemotherapy was prescribed in 147 (76.8%) patients who received systemic treatment. The majority of treatment was with cisplatin (N=132, 70.6%). Sixty-four (13.3%) patients received ≥2 treatment lines. After median 60.5 months of follow-up the 5-year OS in patients with metastatic BC was 2.7%. The 1-, and 3-year OS rates were 31.0% and 9.8%, respectively. Median OS from the start of treatment was 7.3 months (95% CI 6.5-8.1). Conclusions: The results of the OSURK study indicate the need for further implementation of innovative drugs in real practice in order to significantly increase the OS of patients with metastatic BC.

Keywords: Metastatic bladder cancer, 5-year overall survival, treatment, Central Asia

Introduction

Kazakhstan is the ninth largest country in the world, located mainly in Central Asia and partly in Eastern Europe, with a population of 19 million people. Cancer care for the adult population in Kazakhstan is provided by republican organizations JSC “Kazakh Research Institute of Oncology and Radiology”, JSC “National Scientific Cancer Center”, 15 oncology dispensaries/centers, and 5 oncology departments that are part of multidisciplinary clinics. There is a national cancer registry, an electronic registry of cancer patients (IS ERCP), which combines data on all patients with malignant neoplasms, consisting of epidemiological and economic blocks. To improve the phasing and routing of patients, the provision of oncological care in the republic is divided into three levels within the framework of an integrated model. The provision of specialized medical care to cancer patients in the country is included in the guaranteed volume of free medical care and is covered by the state. However, there are internal problems in access to care (rural, elderly or disabled population) in this country.

In 2017, 717 new cases of bladder cancer (BC) were diagnosed in the Kazakhstan with incidence rate 4.0 per 100,000 of the general population. Data on age-standardized rates have only been available since 2017, and the age-standardized incidence in 2017 was 3.8 per 100,000 population [1]. BC is more common in men, accounting for approximately 2.2% of all malignant tumors. For comparison, in 2007

there were 609 cases of primary diagnosed BC with an incidence rate of 3.9 per 100,000 population. Thus, over the decade from 2007 to 2017, the increase in this indicator was 15.1% [1, 2].

Bladder cancer mortality rate in men is significantly higher among than women with rates 2.4 and 0.43 per 100,000 in 2017, respectively. In the general population the standardized death rate was 1.03 per 100,000 in 2017. In the past 10 years, from 2007 to 2017, bladder cancer death rates went down 20.2%, from 2.0 to 1.4 deaths per 100,000.

These statistics include patients with all stages of the disease and real-world data on 5-year overall survival (OS) of patients with metastatic BC is rarely published. To date, there is no information on the OS of patients with metastatic BC in Central Asia.

BC treatments approaches in Kazakhstan are based on EAU, NCCN guidelines and summarize data from randomized clinical trials (RCTs) [3, 4]. In Kazakhstan, international recommendations have been adapted at the national level and the diagnosis and treatment of BC is regulated by the national protocol (Bladder Cancer, approved by the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan dated March 14, 2019, Protocol No. 58). The main general tests that are performed on a patient with BC include a complete blood count, blood chemistry, and urine test. The patient is required to undergo instrumental diagnostic methods including cystoscopy with biopsy. At the same time, histological examination is carried out preferably when performing a transurethral resection of the bladder (TURBT). In case of BC, the level of PD-L1 expression is determined in Kazakhstan since 2021. Additionally, the patient undergoes an ultrasound of the pelvic organs. Intravenous urography is also performed. CT or MRI of the pelvic organs is mandatory and helps to identify a tumor of the bladder, as well as enlarged pelvic lymph nodes and distant metastases.

However, data obtained from RCTs on treatment of BC often does not reflect whole patient population due to strict inclusion criteria to include younger patients with better ECOG PS who are candidates for platinum-based therapy. On the other hand, countries defined by the World Bank as having lower middle-income economies might not always have enough resources to implement best care and therefore, might be in need of resource stratified guidelines. Thus, registries are acknowledged sources of data on real-world OS and the effect of treatment approaches on it [5].

The goals of the OSURK registry study were to assess 5-year OS in patients with metastatic urothelial cancer diagnosed in 2017 in Kazakhstan and collect data on the use of various treatment options in routine clinical practice.

Methods

Patients

Patients were retrospectively identified in the national register of Kazakhstan between January 2017 and January 2018. ERCP is the biggest register in the country and includes patient data from 17 regions. Investigators collected patient information and processed records online on the following data: demographical characteristics, received treatment and outcomes. Collected data was depersonalized and unidentifiable. To be included in the study, patients had to meet the following criteria: newly diagnosed metastatic BC, the presence of histologically confirmed urothelial cancer and age ≥18 years at the time of diagnosis. Patients who had received prior neoadjuvant and adjuvant chemotherapy for non-metastatic BC were also eligible to participate in the study. Patients treated in clinical trials were not included. Patients were followed up using computed tomography or magnetic resonance imaging to the date of death or the last visit if they were still alive.

The OSURK study complied with the rules of the Declaration of Helsinki. The study protocol was approved by the Principal Investigators and Study Group.

Endpoints and assessments

The primary endpoint of this study was 5-year OS. Secondary endpoints included median OS, 1- and 3-year OS rates, overall response rate, patient (age, sex, histological subtype, molecular changes), and TNM stage (UICC, 8th Edition) and treatment (systemic therapy) characteristics.

Disease progression was assessed on the basis of radiological and clinical data, and in addition, change in therapy and death were markers of disease progression. Switching from first-line therapy to subsequent-line therapy have also been studied. Switching to the next line was defined as a change in treatment as a result of disease progression or toxicity. In the medical records of some patients, data on all parameters were not available; available data on these patients were used where appropriate.

Statistical analysis

The design of OSURK study is a retrospective cohort study. Descriptive statistics (means, medians, and proportions) were used to describe baseline patient characteristics and treatment regimens. The survival time was calculated from the day of diagnosis of metastatic BC to the day of death (OS). OS analysis was conducted in the intent-to-treat (ITT) population, comprising all patients who had BC between January 2017 and January 2018 in Kazakhstan. Survival curves were evaluated using the Kaplan-Meier method. The associations between outcomes, demographic factors, and treatment regimens were assessed by Kaplan-Meier analyzes using the log-rank test at a two-sided significance level of 0.05 (all *P*-values are considered exploratory). All statistical analyzes were performed using the IBM SPSS Statistics Base v22.0 software (SPSS, Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Totally 480 adult patients with metastatic BC were included for analysis in this study. The median number of patients per region was 28.2 (1 to 57). All patients had a confirmed metastatic disease. The median age at diagnosis was 70.0 years (range, 30 to 100 years). 57.9% of patients were older than 70 years. Most of the patients were male (N=390, 81.3%).

The histological subtype of BC (urothelial or other) was verified in 197 patients (41%), was not verified in 283 patients (59%) and determined as "BC". The histological subtype was more frequently verified in cancer centers than in regional clinics (136 vs. 61 patients). Molecular diagnostics (PD-L1 and FGFR assessments) were not performed (0%) in 2017. Patient characteristics are presented in **Table 1**.

Treatment patterns

Overall, 187 (39%) patients received systemic therapy for metastatic disease (**Table 1**). Median duration of all lines of therapy was 3.1 months (95% CI 1.2-4.6). Sixty-four (13.3%) patients received ≥2 treatment lines. No significant differences in frequency of systemic therapy in the different age (<70 vs. ≥70) and gender (male vs. female) groups were found (all P>0.1). Platinum-based chemotherapy was prescribed in 147 (76.8%) patients who received systemic treatment. The majority of treatment was with cisplatin (N=132, 70.6%). The most common combination was gemcitabine and cisplatin/carboplatin. Immunotherapy based on checkpoint inhibitors was not used in 2017. The main reason (N=402, 83.8%) for treatment discontinuation included disease progression. There were no treatment-related deaths in the study.

Efficacy outcomes

After median 60.5 months of follow-up the 5-year OS in patients with metastatic BC was 2.7%. The 1-, and 3-year OS rates were 31.0% and 9.8%, respectively. Median OS from the start of treatment was 7.3 months (95% CI 6.5-8.1). When assessing the relationship of survival with the number of treatment lines, OS of patients who received at least one line of therapy (median 12.2 months; 95% CI 11.1-13.2) was significantly longer than those who did not receive treatment (3.7 months; 95% CI 3.4-3.99, P<0.0001, **Figure 1A**). Despite the small number of patients on non-platinum-based therapy, their OS was shorter (median 8 months; 95% CI 7.3-8.7) compared with patients who received platinum-based therapy (14.0 months; 95% CI 11.6-16.4, P<0.0001, **Figure 1B**). The OS of elderly patients did not differ (P=0.77; **Figure 1C**).

Objective response rate assessment was carried out in 131 patients. The overall response rate was 28.2%. All responses were partial. Forty-nine (37.4%) patients had stable disease and 45 (34.4%) had disease progression.

Table 1. Patient and treatment characteristics

Age, years (range)	70 (30-100)
Gender, N (%)	
Male	390 (81.3)
Female	90 (18.7)
TNM stage, N (%)	
I	77 (16.1)
II	159 (33.1)
III	138 (28.8)
IV	65 (13.5)
NA	41 (8.5)
Histological subtype of BC, N (%)	
Verified	197 (41)
History of neoadjuvant/adjuvant chemotherapy, N (%)	
Yes	158 (32.9)
No	322 (67.1)
Systemic therapy for metastatic disease, N (%)	
Yes	187 (39)
No	293 (61)
Duration of systemic therapy (all lines), median. months (95% CI)	3.1 (1.2-4.6)
Platinum-based chemotherapy, N (%)	147 (30.6)
Cisplatin, N (%)	132 (27.5)

NA, data not available.

Discussion

In Kazakhstan, treatment for patients with metastatic BC is discussed by a multidisciplinary team of specialists, which includes urological oncologist, radiation oncologist, medical oncologist, and pathologist. A multidisciplinary approach is practiced in all public clinics. In some cases, regional centers seek advice from comprehensive cancer centers. Since 2021, the standard systemic treatment has been chemotherapy based on a combination of cisplatin and gemcitabine, as well as immunotherapy. Previously, immunotherapy was not approved in Kazakhstan. Due to national characteristics, patients often turn to oncologists when the process is already widespread and the performance status is poor, which can affect the choice of subsequent treatment plan, as well as the ability to carry it out.

The present OSURK study evaluated the survival of patients with metastatic BC based on representative data from all regions of the Kazakhstan, including factors affecting OS. Data from almost 500 patients was collected and analyzed in the OSURK registry study.

The basis of the treatment program for malignant epithelial tumors of the bladder in Kazakhstan is surgical intervention, which allows removal of the tumor mass. As part of complex therapy, taking into account the stage and extent of the process, chemotherapy (including intravesical), radiation and other methods can be performed.

The median OS calculated by the Kaplan-Meier method in the overall study population was 7.3 months, and the 5-year survival rate was 2.7%. The results on OS obtained in the OSURK study were inferior to those to compare with developed countries. Thus, in the real practice register in Denmark, which included 952 patients in 2017-2019, the median OS was 11.7 months [5], in Germany, in the register with the inclusion of 435 patients in 2016 [6], it was 16.1 months, and, finally, in the US registry containing information on 1,811 patients for 2011-2017, it was 12.7 months [7]. According to the SEER 17 2012-2018 database, the 5-year survival rate for patients with advanced BC in the United States was 7.7% [8]. It should be noted that in these countries a large number of patients received chemotherapy, mainly gem-

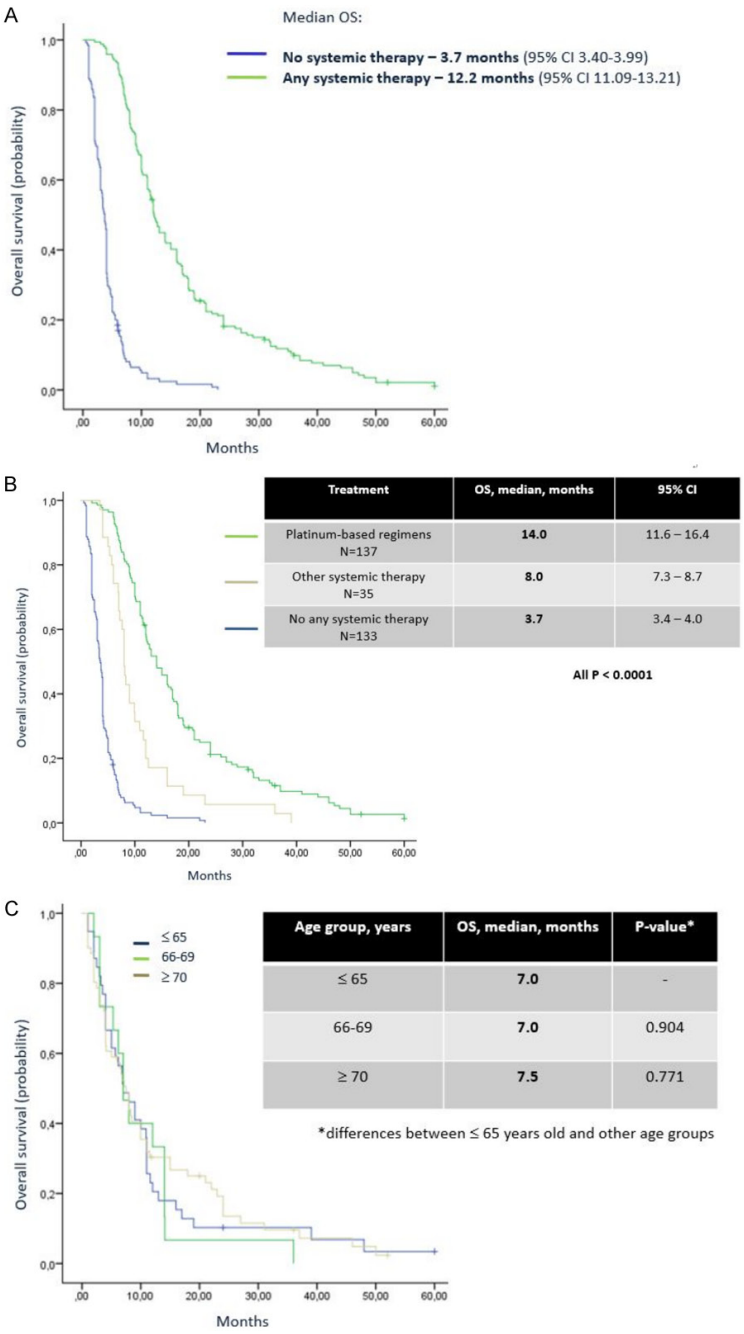

Figure 1. Overall survival in cohorts. A. Patients with or without systemic therapy; B. Different treatment options; C. Different age groups.

citabine and cisplatin. In addition, in the US study, atezolizumab was used as second-line therapy in 13% of patients. Nevertheless, even in developed countries, the results of survival cannot be called impressive 4-5 years ago, which is due to the aggressiveness of the disease and relatively recent access to immuno- and targeted therapy in daily practice.

In a large registry study IMPACT UC with the inclusion of 18,888 patients for 2014-2019, the prescription of first-line drugs was analyzed [8]. The authors concluded that cisplatin-based combinations were more often prescribed to younger patients with a lower comorbidity index, while the use of cisplatin led to the best outcome of OS. Therefore, disease symptoms, age, and comorbidities may limit the use of recommended options in first-line therapy. In our study, we also found the best outcome in patients receiving cisplatin. The modest OS rates in the OSURK study may be explained by the insufficient use of systemic therapy in only a third of patients (39%), the rare use of second- and subsequent-line therapy in patients with disease progression (34.2%), and the absence of novel drugs approvals (avelumab, pembrolizumab, nivolumab, atezolizumab, and erdafitinib) in the Kazakhstan at that time. The same problems were observed in other BRICS countries [9-11], where only 20% of patients with genitourinary cancers receive second-line therapy and immunotherapy. According to the Russian registry URRU, the median OS of patients with metastatic BC was 7 months and 3-year survival rate was 10.6%, which is very similar to our study results [12].

Improving oncological care in the country is carried out as part of the implementation of the tasks of the Comprehensive Plan to Combat Cancer in the Republic of Kazakhstan for 2018-2022, approved by the Decree of the Government of the Republic of Kazakhstan dated June 29, 2018 No. 395. The purpose of the Comprehensive Plan is to reduce the burden of malignant neoplasms. The comprehensive plan includes the development of preven-

tion and management of risk factors, highly effective early diagnosis of malignant neoplasms, and the introduction of an integrated model of medical care that provides cancer patients with access to the latest high-tech personalized methods for the prevention, diagnosis and treatment of malignant neoplasms, including bladder cancer. In addition, novel agents improve outcomes but also increase costs, so further challenges for urothelial cancer care in constrained-resource settings are envisioned.

Based on clinical trials data the use of novel options in first-line therapy can significantly improve survival. The prospective Phase 3 JAVELIN Bladder 100 study included a total of 700 patients who did not have disease progression with first-line chemotherapy [13]. Patients were randomly assigned to receive either avelumab, an anti-PD-L1 antibody, or best supportive care. The primary endpoint was OS in the general population and in patients with PD-L1 positive tumors. One-year OS rate was 71.3% in the avelumab group and 58.4% in the control group, and the median overall survival was 21.4 months compared to 14.3 months. Avelumab also significantly prolonged OS in the PD-L1-positive population (30.9 vs. 18.5 months) [14], although testing of PD-L1 expression in a national program does not seem appropriate in BC patients [15].

Therefore, using new approaches in routine practice in the Kazakhstan can lead to a significant increase of OS in patients with metastatic urothelial cancer. Access to new medicines is free, but it is important to consider whether this access can reach all patients at a high cost of treatment and a limited budget.

The limitations of the study are a retrospective design and a heterogeneous sample of the population, which makes it difficult to conduct a multivariate analysis to assess the influence of factors on survival. Variety of nationalities living in Kazakhstan could possibly be another source of bias.

In conclusion, the results of the OSURK study indicate the need for further implementation of innovative drugs in real practice in order to significantly increase the OS of patients with metastatic BC. Unless there are contraindications to cisplatin-based therapy, patients should receive treatment regardless of age. In addition, there was the significant correlation between increased survival and treatment after first-line therapy. This is especially important in developing settings due to access to second-line therapy is not standardized.

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Disclosure of conflict of interest

None.

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