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14

Chemotherapy for Metastatic Disease

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1. Introduction

Bladder cancer occurs with a relatively high incidence in industrial nations. For example, bladder cancer is the fourth most common type of cancer in American men. The estimated U.S. incidence in 2008 was 68,810 cases and the mortality was 14,100 cases (Jemal et al., 2008). Of newly diagnosed bladder cancer cases, approximately 70% - 80% will present with non muscle-invasive disease. Among such cases, 50% - 70% will recur, and 10% - 30% will progress to muscle-invasive disease (Soloway et al., 2002; Saad et al., 2002). Radical cystectomy with or without chemotherapy is the standard therapy for muscle-invasive disease; however, some patients will experience metastatic relapse after radical surgery. A few patients present with metastatic disease upon their initial presentation at the hospital. Such advanced bladder cancer remains an incurable terminal disease, and accounts for 3% of the cancer-related mortality in the United States. Deaths from bladder cancer are mainly related to distant spread; hence, prevention of metastatic disease remains a crucial goal in this disease. Systemic chemotherapy achieves palliation, survival benefit, and occasional long-term remissions. For the last two decades, cisplatin-based combination therapies have evolved as the standard. The MVAC regimen (Sternberg et al., 1988) was reported to demonstrate an impressive complete remission rate of 37% in advanced urothelial carcinoma (UC), and in a subsequent comparative study was found to be superior to the single agent cisplatin (Saxman et al., 1997). In this chapter, we review the recent progress in chemotherapeutic regimens not only for advanced bladder cancer, but also for advanced UC in the upper urinary tract. We also show current data on the efficacy of combination therapy with gemcitabine and platinum anti-cancer drugs, which is mainly used as a second-line treatment in our institution.

2. The first successful chemotherapeutic regimen for advanced Urothelial Carcinoma (UC)

Despite recent developments in anti-cancer drugs, advanced UC remains an incurable disease, with a median survival time of only 12 to 14 months (Jemal et al., 2003). The most reliable treatment option for advanced UC is considered to be combination chemotherapy including a platinum anti-cancer drug. The combination chemotherapy regimen of methotrexate / vinblastine / doxorubicin / cisplatin (MVAC) as reported originally by Sternberg (Sternberg et al., 1988) is currently being used worldwide with superior efficacy. However, MVAC treatment is associated with substantial toxicities and has a toxic death rate of approximately

3 - 4% (Sternberg et al., 1989; Loehrer et al., 1992). Therefore, the need for an alternative less toxic combination chemotherapy that can provide efficacy similar or superior to the MVAC regimen has been identified. Gemcitabine, a nucleoside analogue, has demonstrated activity against a range of solid tumors, including metastatic UC (Gatzemeier et al., Moore, 1996; Stadler et al., 1997). In particular, gemcitabine alone has yielded a response rate of 23 - 29%, with a complete response rate of 4 - 13%, in both previously treated and untreated metastatic UC patients (Sternberg, 2000). The good activity and toxicity profiles of single-agent gemcitabine treatment and its synergism with cisplatin in pre-clinical models (Peters et al., 1995) led to the development of this combination for the treatment of advanced UC. After obtaining results from phase 2 trials of combination therapy comprising gemcitabine plus cisplatin (GC) as first- or second-line treatment for UC, von der Maase et al. published a large multinational phase 3 trial comparing MVAC with GC therapy, with a total of 405 patients accrued (von der Maase et al., 2000). The final results show that the two regimens are similar in terms of response rate, time to progression and survival. However, the GC combination showed a better safety profile and tolerability than MVAC. The representative randomized trials on MVAC and GC are summarized in Table 1. Carboplatin shares a common mechanism of action with cisplatin, but the two have different pharmacokinetic and dose-limiting toxicities (Van Echo et al., 1989). Patients with UC are often elderly, and frequently have clinical or subclinical renal function impairment. Thus, the substitution of carboplatin for cisplatin offers a promising alternative for these patients. There have been several phase 2 reports showing that gemcitabine / carboplatin achieved clinical results equivalent to those of GC (Xu et al., 2007; Dogliotti et al., 2007). It can thus be speculated that the combination of gemcitabine plus a platinum anti-cancer drug (cisplatin or carboplatin) is currently being used worldwide in the treatment of advanced UC.

Therapy	No. of Patients	Response Rate/PFS	Median Survival	Hazard Ratio/*P* value
MVAC (Sternberg)	263 (MVAC + High dose MVAC)	50 % (CR 9 %) Med PFS 8.1 months	14.9 months (2 year survival 26.2 %) (5 year survival 13.5 %)	HR = 0.76 *P* = 0.042
High dose MVAC (Sternberg)		64 % (CR 21 %) Med PFS 9.5 months	15.1 months (2 year survival 36.7 %) (5 year survival 21.8 %)	
Cisplatin (Saxman)	122	PR 12 % Med TTP 10 months	8.2 months	*P* = 0.0002
MVAC (Saxman)	133	PR 39 % Med TTP 4.3 months	12.5 months	
MVAC (Von der Maase)	202	46 % Med PFS 8.3 months	15.2 months	*P* = 0.75 HR = 0.042
GC (Von der Maase)	203	49 % Med. PFS 7.7 months	14.0 months	

Table 1. Summary of representative randomized trials exploring chemotherapy in metastatic urothelial cancer

3. The efficacy and safety of combination chemotherapy with gemcitabine and a platinum anti-cancer drug. A regimen mainly used as second-line chemotherapy for patients with advanced UC at Tottori university hospital

Our original data regarding the effects of combination therapy with gemcitabine plus platinum anti-cancer drug as second-line chemotherapy for cases of advanced UC are described below. These data were gathered mainly as a result of limitations in the Japanese insurance system, which until recently did not cover the use of gemcitabine for the treatment of UC. That is, before February 2009, the use of gemcitabine was not allowed for general use in Japan, and thus only referral academic institutions such as ours were able to conduct gemcitabine therapy. Because the incurable rate is still high in advanced UC patients to date in spite of the medical progress of many anti-cancer drugs in Japan and other countries, physicians often encounter patients with advanced UC who need to undergo more than one kind of chemotherapy. Therefore sequential data of second-line chemotherapy like ours is considered to be useful for urological oncologists worldwide. In this paragraph, the therapeutic data for cases of upper urinary tract UC are also included. This book is of course about bladder cancer; however, it is often difficult to isolate the therapeutic data for bladder cancer from the data for all cases of UC. Therefore, we regret that we cannot describe the results for bladder cancer data specifically.

3.1 Patients' characteristics

From December 2004 until September 2011, 30 patients received the combination chemotherapy of gemcitabine plus a platinum anti-cancer drug (cisplatin or carboplatin) at

Characteristics	No. of patients (%)
No. of patients	30 (100%)
Median age, yr (range)	72 (52-83)
Gender	
Male	23 (76.7%)
Female	7 (23.3%)
Previous therapy	
None	4 (13.3%)
Methotrexate/Epirubicin/Cisplatin (MEC)	14 (46.7%)
Methotrexate/Epirubicin/Carboplatin (modified MEC)	9 (30.0%)
Etoposide/ Cisplatin	1 (3.3%)
Radiation + Intraarterial chemotherapy	2 (6.7%)
Primary urothelial tumor site	
Bladder	9 (30.0%)
Renal pelvis ~ ureter	21 (70.0%)
Advanced disease at first visit	7 (23.3%)
Recurrence after surgery for primary tumor	23 (76.7%)
Site of metastasis or recurrence, or invasion from primary tumor	
Lung	6 (20.0%)
Lymph node	18 (60.0%)
Local recurrence	5 (16.7%)
Bone	2 (6.7%)

Table 2. Patient characteristics

our institution. All patients were evaluated for efficacy and for toxicity. The pretreatment characteristics of the patients are listed in Table 2. 23 patients (77%) had previously received combination chemotherapy of methotrexate / epirubicin / cisplatin (MEC).

3.2 Treatment plan

In the first cycle of the therapy, the creatinine clearance (Ccr) (ml / min) of each patient was measured prior to initiation of the therapy. In the patients with Ccr > 60, cisplatin was administered, while in those with Ccr < 60, carboplatin was administered as the platinum anti-cancer drug. Gemcitabine (1,000 mg / m^2) was given by intravenous infusion over 30 – 60 min on days 1, 8, and 15. Cisplatin (70 mg / m^2) was given by intravenous infusion over 30 – 60 min on day 2 in the cisplatin group, whereas carboplatin dosed to an AUC of 5 was given by intravenous infusion over 30 – 60 minutes on day 2 in the carboplatin group. Basically, each cycle consisted of 21 days. However, an extension of the days in each cycle was permitted based on the judgment of the physician in charge if any severe adverse events were noted. All toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Dose adjustment during the treatment was based on hematological and non-hematological assessment of toxicities. In the hematological assessment of toxicities, leukocyte and platelet counts were generally measured weekly. For cases where leukocytes < 2,000 / mm^3 or platelets < 75,000 / mm^3, or where there was evidence of bleeding, gemcitabine was omitted. No new cycle was started unless leukocytes were > 2,000 / mm^3 and platelets were > 75,000 / mm^3. The platinum anti-cancer drug dose was reduced by 50% for grade 2 neurotoxicity, omitted for grade 3, and stopped for grade 4. For renal toxicity, the dose of platinum anti-cancer drug was reduced by 50% for Ccr 50 – 59, and omitted for Ccr < 50. For other grade 3 non-hematological toxicities (except nausea, vomiting, and alopecia), gemcitabine and platinum anti-cancer drug doses were reduced by 50% or omitted per the physician in charge. For grade 4 toxicities, doses were reduced by 50% or stopped (unless the patient was responding to the therapy).

3.3 Dose administration

The median number of consecutive cycles per patient was 3 (range: 1 – 7). 16 patients (53%) underwent more than 3 cycles of the therapy. Cisplatin was administered in 12 patients (40%), while carboplatin was administered in 18 patients (60%) as the platinum anti-cancer drug (Table 3).

3.4 Efficacy

All 30 patients were assessed with regard to clinical outcome and treatment efficacy according to RECIST criteria at the end of the study. With regard to clinical outcome (Table 3), we observed 2 (7%) cases of complete response (CR) and 7 (23%) cases of partial response (PR), with an overall response rate (ORR) of 30%. The visceral field of metastasis or relapse in patients of CR and PR was the lungs in 3 cases, lymph nodes in 5 cases, and local relapse (post-nephroureterectomy) in 1 case. There were no cases with responses in other visceral fields such as bone. Stable disease (SD) was identified in 10 patients (33%), and progressive disease (PD) in 9 patients (30%). 2 patients (7%) were not evaluated. The median time to follow-up was 11.7 months (range: 0.8 – 65.8 months). The median overall survival (OS) was 11.1 months. Kaplan-Meier curves for OS are shown in Fig. 1.

		No. of patients (%)
No. of chemotherapy cycles	1	6 (20.0)
	2	8 (26.7)
	3	10 (33.3)
	More than 4	6 (20.0)
Platinum drug	Cisplatin	12 (40.0)
	Carboplatin	18 (60.0)
Efficacy according to RECIST	CR	2 (6.7)
	PR	7 (23.3)
	SD	10 (33.3)
	PD	9 (30.0)
	NE	2 (6.7)
Outcome	NED	2 (6.7)
	Alive with cancer	8 (26.7)
	Dead due to cancer	20 (66.6)

Table 3. Treatment profile and efficacy

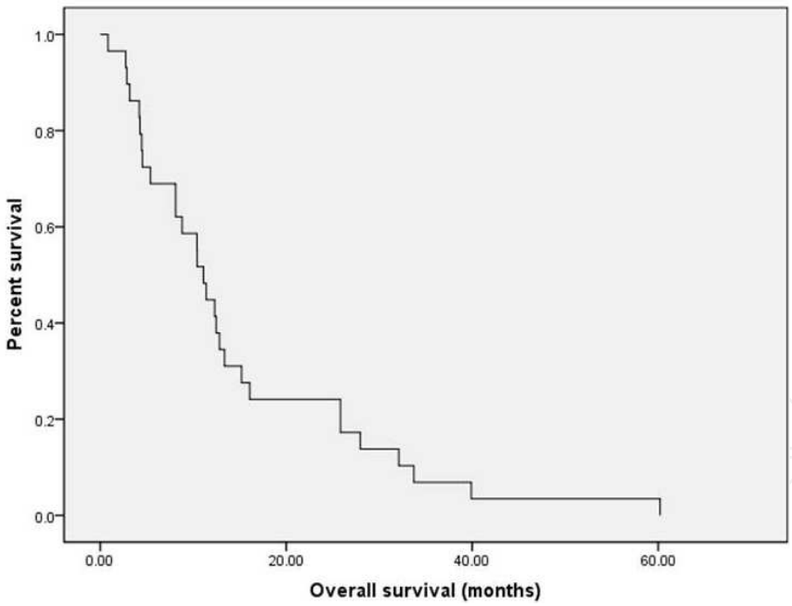

Fig. 1. Overall survival rate of all 30 patients with advance UC treated at Tottori University Hospital

3.5 Toxicity

Only 1 patient discontinued the therapy simply for reasons of toxicity; this patient showed a Grade 2 allergic reaction to gemcitabine, which was administered on day 15. Since this patient eventually received one whole cycle of the therapy, we assessed the efficacy of the

treatment as such. Grade 3 / 4 neutropenia was the most frequent toxicity, occurring in 63% of the patients. Grade 3 / 4 thrombocytopenia was also a frequent toxicity, occurring in 57% of the patients. Grade 3 / 4 non-hematologic toxicities included nausea and vomiting in 1 patient (3%). Major toxicities according to NCI-CTC are summarized in Table 4. No other types of major toxicities such as nephrotoxicity or neurotoxicity were observed in any patients. In order to analyze the cumulative damage due to hematologic side effects, the nadir values of blood counts were analyzed. The nadir values of hemoglobin and the nadir counts of leukocytes and platelet cells in the first cycle were practically the same as those in the other progressive cycles. In other words, hematological toxicities were not enhanced by the progressive repetition of cycles (data not shown).

	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4 (13.3)	6 (20.0)	16 (53.3)	3 (10.0)
Anemia	3 (10.0)	13 (43.3)	9 (30.0)	4 (13.3)
Thrombocytopenia	6 (20.0)	4 (13.3)	8 (26.7)	9 (30.0)
Vomiting	3 (10.0)	2 (6.7)	1 (3.3)	0 (0)
Allergy	0 (0)	1 (3.3)	0 (0)	0 (0)

Table 4. Mayor toxicities according to NCI-CTC

3.6 Conclusions

The efficacy of gemcitabine plus a platinum anti-cancer drug as a second-line chemotherapy for advanced UC was found to be modest. The toxicity of the therapy was tolerable despite damage from previous chemotherapy and repeated cycles. The present data, obtained as a result of particular limitations in the medical insurance industry in Japan, will be helpful when considering the best course of second-line chemotherapy for cases of advanced UC in the future.

4. Is there any effective combination chemotherapy except MVAC or GC for advanced UC?
— The combination therapy of methotrexate / epirubicin / cisplatin (MEC) —

The combination chemotherapy of methotrexate, epirubicin and cisplatin (MEC) was mainly developed in Japan for the purpose of establishing a regimen less toxic than MVAC but with equal efficacy. Several academic Japanese institutions including the Japanese Urothelial Cancer Research Group promoted a randomized trial comparing MEC and MVAC (Kuroda et al., 1998). Total of 89 patients were assigned to three groups receiving either standard MEC (S-MEC), dose-intensified MEC (I-MEC) or MVAC. The S-MEC regimen consisted of methotrexate (30 mg / m^2), epirubicin (50 mg / m^2) and cisplatin (100 mg / m^2), and that of the I-MEC regimen was methotrexate (36 mg / m^2), epirubicin (60 mg / m^2) and cisplatin (120 mg / m^2). In both groups, methotrexate was administered on day 1 and 15, epirubicin was administered on day 1, and cisplatin was administered on day 2. In the I-MEC group, G-CSF

(2μg / kg) was administered from day 3 until day 12 routinely. The response rates (CR + PR) were 52% with S-MEC, 76% with I-MEC and 47% with MVAC. All of the adverse events were rendered tolerable in the S-MEC and I-MEC groups through the use of G-CSF agents. We had been utilizing MEC as a first choice therapy until 2008 in our institution because it was less toxic than but as effective as MVAC. As a matter of fact, most of the patients in our study of second-line combination chemotherapy with gemcitabine and the platinum anti-cancer drugs described above had been receiving MEC as the first line chemotherapy at other institutions.

5. Prevention of micro metastasis and effort of tumor reduction by neoadjuvant chemotherapy at radical cystectomy

In T2-4 (invasive) bladder cancer, neoadjuvant chemotherapy with MVAC or cisplatin, methotrexate, and vinblastine has demonstrated significant progression-free survival (PFS) and OS benefit in several randomized trials. One representative trial is the Intergroup 8710 trials reported by Grossman et al. in which cystectomy alone was compared with neoadjuvant MVAC followed by radical cystectomy. The group receiving neoadjuvant chemotherapy had an increased likelihood of eliminating residual cancer in the cystectomy specimen (pT0) and had an associated improved survival. Moreover, neoadjuvant chemotherapy did not adversely affect the patient's chance of undergoing a cystectomy and did not increase the risk of postoperative complications (Grossman et al., 2003). In the combined analysis of 2 Nordic studies, neoadjuvant platinum-based combination chemotherapy was associated with an 8% increase in survival at 5 years (Sherif et al., 2004). A meta-analysis of randomized controlled trials demonstrated a survival benefit to receiving neoadjuvant chemotherapy (Winquist et al., 2004). Carboplatin-based regimens have been evaluated in the neoadjuvant setting only in phase 2 trials, and hence their use in the neoadjuvant or adjuvant setting cannot be recommended (Smith et al., 2008; deVele White et al., 2009). The studies of adjuvant chemotherapy have demonstrated conflicting results. They have had design flaws and small sample sizes and are therefore underpowered to give a conclusive answer regarding the benefits.

6. Other recent chemotherapeutic regimens including taxanes

The taxanes are diterpenes produced by the plants of the genus Taxus (yews), and include such compounds as docetaxel and paclitaxel, the latter of which was originally derived from the Pacific yew tree. The principal mechanism of action of the taxane class of drugs is the disruption of microtubule function. Microtubules are essential to cell division, and taxanes stabilize GDP-bound tubulin in the microtubule, thereby inhibiting the process of cell division. Thus, in essence, taxanes are mitotic inhibitors. Both paclitaxel and docetaxel have been studied as chemotherapeutic agents for metastatic bladder cancer. Paclitaxel-based regimens in combination with either cisplatin or carboplatin have been evaluated with response rates between 16% and 36% and median survival ranging from 6 to 10 months depending on the characteristics of the patients enrolled and whether they are ciplatin-sensitive or a refractory population (Vaishampayan et al., 2005; Uhm et al., 2007). A phase 3 study comparing docetaxel and cisplatin (DC) with G-CSF versus MVAC with G-CSF found MVAC to be more effective than DC for metastatic cancer; MVAC demonstrated both a superior median time to progression (9.4 vs 6.1 months; $P = 0.003$) and median survival time (14.2 vs 9.3 months; $P = 0.026$) (Bamias et al., 2004). Other recent representative reports of taxanes with cisplatin therapy are shown in Table 5. Antifolates such as trimetrexate and

premetrexed have been better tolerated with promising response rates and should be promising for future evaluation (Witte et al. 1994; Sweeney et al., 2006). Oxaliplatin-based regimens have been evaluated and also shown to be of modest benefit (Carles et al., 2007).

Author	Previous therapy	Dose (mg / m²)		No. of Cases	Efficacy (%) (CR + PR)	CR rate (%)	Median survival (M)
		Cisplatin	Taxane				
Dreicer	None	75	175 (P)	52	50	8	10.6
Burch	None	70	135 (P)	34	70	32	13
Sengelov	None	75	75 (D)	25	60	26	13.6
Dimopoulos	None	75	75 (D)	66	52	12	8

P, Paclitaxel; D, Docetaxel

Table 5. Recent representative reports of taxanes with cisplatin therapy for advanced urotherial cancer

7. Role of targeted therapies in bladder cancer

The actual clinical advent of targeted therapies has been slower in UC, as compared to other solid tumors due to large variations in histology worldwide, as well as the difficulty in accruing to clinical trials with this malignancy. Vaishampayan et al. evaluated and reported the frequency of overexpression of Her-2 in bladder cancer and correlated with the Her-2 expression in metastatic sites. Interestingly, the overexpression of her-2 by immunohistochemistry (IHC) (2+ or 3+) was 37% in primary bladder tumor tissue, the expression in metastatic sites such as lymph nodes was 63% and the expression in visceral metastases was 86% (Vaishampayan, 2009). 45% of Her-2/neu-negative primaries had Her-2/neu-positive lymph node metastases, while 92% of Her-2-positive primary tumors were associated with Her-2-positive metastasis. This finding suggested that Her-2 over-expression could be a useful therapeutic target for advanced UC. Hence, a phase 2 trial was conducted and reported evaluating the role of trastuzumab with chemotherapy in metastatic UC. An extremely promising 70% response rate and a favorable median survival of 14 months were noted despite 55% of the patients having visceral metastases (Hussain et al., 2007). Another novel approach using molecular targeted therapy for advanced UC patients is the combination therapy of bevacizumab and chemotherapeutic agents. A phase 2 study of bevacizumab in combination with cisplatin and gemcitabine in metastatic or locally advanced bladder cancer involving 36 patients showed a complete response in 6 (17%), and a partial response in 18 (50%); this combination is now being studied in a phase 3 trial (Dovedi & Davies, 2009; Hahn et al., 2011). Another study with anti-angiogenic therapy is the evaluation of sunitinib in a placebo-controlled double-blind trial with the goal of sustaining or prolonging response, after initial chemo-therapy in advanced bladder cancer (Bradley et al., 2007). Epithelial growth factor receptor has also been identified as an exciting target in UC. The over-expression of EGFR by IHC is noted in about 92% (35 of 38) of the bladder cancer cases at Wayne State University; however, its association with survival

outcome has not been established (Bellmunt et al., 2003). Given the possibility of EGFR-targeted therapy, a phase 2 randomized trials of cisplatin and gemcitabine with or without cetuximab (a monoclonal antibody to EGFR) is ongoing as a frontline therapy for metastatic UC. Current and future additional trials of targeted therapy are listed in Table 6.

First line for metastatic disease	Therapy	Organization
(not renal insufficiency)		
Phase Ⅱ	GC + BVZ	CALGB
Phase Ⅱ	GC + Sorafenib	MSKCC, EORTC
Phase Ⅰ	GC + Lapatinib	EORTC
First line metastatic disease		
(renal insufficiency)		
Phase Ⅱ	GEM + CBDCA + BVZ	MSKCC
Phase Ⅱ	Sunitinib	SOGUG
Second line		
(single agent)		
Phase Ⅱ	Sunitinib	MSKCC
Phase Ⅱ	Sunitinib randum	U. Michigan
Phase Ⅱ	Sorafenib	PMH/SWOG

GC, gemcitabine + cisplatin; BVZ, bevacizumab; GEM, gemcitabine; CBDCA, carboplatin; CALGB, Cancer and Leukemia Group B; MSKCC, Memorial Sloan-Kettering Cancer Center; EORTC, European Organization for Research and Treatment of Cancer; SOGUG. Spanish Oncology Genitourinary Group; U. Michigan, University of Michigan; PMH, Princess Margaret Hospital; SWOG, Southwest Oncology Group

Table 6. Current and future trial with targeted therapy

8. Conclusions

Since the breakthrough progress of development MVAC chemotherapy by Sternberg for advanced UC patients, the survival of such patients has been prolonged compared with those of untreated patients. However, despite the development of anti-cancer drugs, metastatic bladder cancer is still not considered a curable disease. Numerous efforts to achieve improved curability are going, including investigations into molecular targeted therapy, which has just been developed as a breakthrough treatment for patients with advanced renal cell carcinoma in the same field of urologic oncology.

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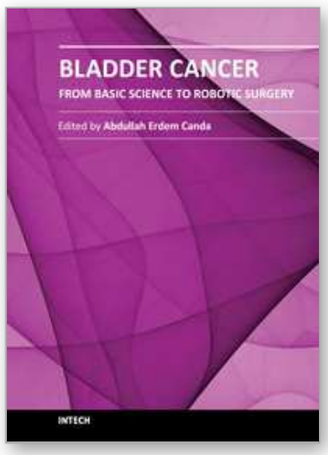

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This book is an invaluable source of knowledge on bladder cancer biology, epidemiology, biomarkers, prognostic factors, and clinical presentation and diagnosis. It is also rich with plenty of up-to-date information, in a well-organized and easy to use format, focusing on the treatment of bladder cancer including surgery, chemotherapy, radiation therapy, immunotherapy, and vaccine therapy. These chapters, written by the experts in their fields, include many interesting, demonstrative and colorful pictures, figures, illustrations and tables. Due to its practicality, this book is recommended reading to anyone interested in bladder cancer.

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