Treatment Regimens of Urinary Bladder Adenocarcinoma

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
Brac University
July 2023

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Treatment Regimens of Urinary Bladder Adenocarcinoma" submitted by Ayndrila Tarafder (18346076), of Fall, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

This dissertation focuses on the treatment regiments of urinary bladder adenocarcinoma. Specifically, we assess the effects of various drug-based therapy regimens on the survival and response rates of individuals with this cancer and present a comparative analysis among them. This dissertation addresses the analysis by reviewing existing studies and related clinical trials from the literature. In general, this dissertation can be divided into three independent but interrelated sections. First, we present epidemiology, classification, and histological features of common urinary bladder adenocarcinomas. Second, we review existing treatment regimens by dividing them as non-surgical, surgical, and other treatment options. Further, we group the drug combinations corresponding to non-surgical methods as either cisplatin-based or not. Finally, we develop a comparative analysis among different treatment plans. Based on the comparative analysis, we show that the efficacy of cisplatin-based drugs is better than other drug-based prescriptions for treating urinary bladder adenocarcinoma.

Keywords: Bladder; Adenocarcinoma; Cisplatin; Treatment

Dedication

Dedicated to my beloved parents.

Acknowledgement

First and foremost, I would like to express my gratitude to God. Without His unbounded blessings, I could not accomplish this feat. Then, I want to express my gratitude to my supervisors, Dr. Mohd. Raeed Jamiruddin and Dr. Shahana Sharmin. Without their unwavering support and guidance, this dissertation would not have been possible. They have motivated and supported me throughout my journey at Brac University, especially when I needed it the most. I could not cherish a better advisor, both as a mentor and a person.

My sincere appreciation goes to my respected teachers, especially Professor Dr. Eva Rahman Kabir, Dean, School of Pharmacy, Brac University and Dr. Hasina Yasmin, Professor, School of Pharmacy, Brac University, for their time and insightful feedback on this thesis.

Table of Contents

List of Tables

List of Figures

List of Acronyms

OS	Overall Survival
PFS	Progression Free Survival
MVAC	Methotrexate + Vinblastine + Adriamycin + Cisplatin
MVP	Methotrexate, Vinblastine, and Cisplatin
TIP	Paclitaxel, Ifosfamide, and Cisplatin
GC	Gemcitabine plus Cisplatin
FU	Fluorouracil
FOLFOX4	Fluorouracil, Leucovorin, and Oxaliplatin TB
TC	Paclitaxel + Carboplatin
VI	Etoposide + Ifosfamide

Chapter 1

Introduction

Cancer is a disease in humans that relates to the uncontrolled cell growth and spread in the body (Weinberg, 1996). It has been one of the deadliest diseases of this century with respect to progression and fatality (Devasena et al., 2018). Around tens of millions of people are diagnosed with this deadly disease worldwide each year, with half of them eventually dies (Ma et al., 2006). As a result, it has drawn significant attention from diverse research communities (Popov et al., 2023; Duchesne et al., 2000).

Broadly, most common cancers can be divided into three major types: carcinomas, sarcomas, and leukemias or lymphomas (Cooper et al., 2022). Among them, carcinoma is the most common type of cancer contributing to 90% of all cases (Cooper et al., 2022). Carcinoma is defined as a type of cancer that forms in the epithelial tissue of the body (Cooper et al., 2022). Among different carcinomas, adenocarcinoma is a subtype that has been specifically studied by scientists for its prevalence and fatality (Ryan et al., 2014; Dadhania et al., 2015). Typically, adenocarcinoma develops in glandular tissue, the lining of some internal organs and the site of the production and release of a variety of bodily fluids and chemicals, including mucus (Popov et al., 2023; Susmano et al., 1971). Adenocarcinoma can affect the lung, breast, esophagus, stomach, colon, rectum, pancreas, prostate, and uterus (Ryan et al., 2014; Tsironis et al., 2018; Schuller, 2002).

Carcinoma can develop in many organs of the human body including urinary bladder (Duchesne et al., 2000; Dadhania et al., 2015). The urinary carcinoma of the bladder (UCB) has numerous histologic subtypes (Moschini, 2017). Among them, adenocarcinoma of the urinary bladder is an uncommon variant that accounts for only 0.5% to 2% of all malignant

bladder tumors (Popov et al., 2023). However, compared to typical urothelial carcinoma, bladder adenocarcinoma is linked to more advanced pathologic stages and worse patient survival rates, which necessitates the creation of prognostic tools for patients (Rogers et al., 2006).

The formation of the urinary bladder adenocarcinoma is thought to be caused by metaplastic potential alterations of unstable urothelium (Allen et al., 1965). The researchers also proposed that the metaplastic potential of the urothelium has two different patterns (Mostofi, 1954). In one pattern, cystitis cystica develops because of the hyperplastic epithelial buds' progressive invasion of the lamina propria (Von Brun's nests) (Zaghloul et al., 2006). In another pattern, cystitis glandular, a premalignant condition, is subsequently produced when the urothelial lining of these cysts metaplasias into columnar mucin-producing cells (Kittredge et al., 1964). The causes of the changes are assumed to be chronic vesical irritation and infection (Allen et al., 1965; Mostofi, 1954).

Urinary bladder adenocarcinomas can be categorized as either primary or secondary based on the origin (Dadhania et al., 2015; Zaghloul et al., 2006; Uhlig et al., 2018). Among them, the primary urinary bladder adenocarcinoma is an uncommon subtype (Uhlig et al., 2018). The tumor that causes primary urinary bladder adenocarcinomas is typically exceedingly aggressive which results in other metastatic disease at the time of diagnosis (Zaghloul et al., 2006). As it is frequently found in the mucosa next to primary adenocarcinomas of the urinary bladder, it has been assumed that intestinal metaplasia is a precursor lesion (Kim et al., 2018). On the other hand, carcinomas in other locations such as colorectum, prostate, endometrial, cervix, can contribute to secondary bladder adenocarcinomas (Dadhania et al., 2015). The secondary bladder adenocarcinomas are more common compared to the primary adenocarcinomas, however, metastasis to the bladder is not prevalent (Bates et al., 2000;

Melicow, 1955; Cormio et al., 2014). Since the prognosis and treatment choices for primary versus metastatic adenocarcinoma differ significantly, it is important to correlate the clinical, imaging, histologic, and immunohistochemical data when making this diagnosis (Bates et al., 2000).

Treating urinary bladder adenocarcinoma has always been a challenge for clinicians for the lack of a proper treatment plan (Tsironis et al., 2018; Tatli et al., 2015). To encounter this problem, numerous researchers have studied this disease to identify and develop an efficient treatment plan (Kim et al., 2018; von der Maase et al., 2000; Hong et al., 2009). As a result, there exists a large body of literature related to the development and clinical trial of drugs that can be used to treat urinary bladder adenocarcinoma (Tatli et al., 2015; Yu et al., 2015; Galsky et al., 2007; Johnson et al., 1972). However, none of these studies could single out a treatment plan that outperforms others in terms of all performance metrices. Furthermore, it becomes difficult for clinicians and researchers to navigate through this large volume of literary works. Hence, a systematic review of the existing treatment regiments can contribute to the future research in this direction as well as effective patient management.

1.1 Objective of this Dissertation

The objective of this dissertation is to present a systematic review of the literature of the urinary bladder adenocarcinoma. The dissertation approaches the review by categorizing the literary works based on the survival rate, response rate and corresponding treatment regimens. The dissertation contributes to the existing literature by developing a relationship among treatment regimen and survival and/or response rate for existing studies in the literature.

Chapter 2

Epidemiology

The prevalence of urinary bladder adenocarcinoma is increasing day by day, particularly in developed countries (Bray et al., 2018). Exposure to toxic chemicals in environment and at work poses higher risk to bladder cancer. The main contributor of the bladder cancer is urothelial cells' exposure to potentially mutagenic environmental chemicals (Mushtaq et al., 2019). These exposed urothelial cells cause approximately 90% of the bladder cancer in industrialized areas (Mostafa et al., 1999). On the other hand, squamous cell bladder cancer is a less frequent form of the disease. This form of bladder cancer may be linked to schistosomiasis, a parasite infection that is commonly found in Africa (Mostafa et al., 1999).

Another significant risk factor of bladder cancer is tobacco smoke (Bray et al., 2018). Men possess a higher risk of bladder cancer as they have greater exposure to cigarette smoke. Typically, bladder cancer affects people of 65 years or higher as the disease grows over several decades. Finally, there exists tiny but significant heredity component of this fatal disease (Mushtaq et al., 2019).

Chapter 3

Classification and Histological Features

Adenocarcinoma of the urinary bladder is a relatively uncommon cancer that may first develop in the bladder or may spread from organs as a secondary tumor (Bates et al., 2000). Enteric, mucinous, signet-ring cell, mixed, and not otherwise specified (NOS) growth patterns are some examples of the various growth patterns that define primary bladder adenocarcinoma (Dadhania et al., 2015). On the other hand, colorectal, prostate, endometrial, cervicovaginal, and other sites may give rise to secondary bladder adenocarcinomas (Bates et al., 2000; Melicow, 1955). Apart from these, urachal and clear cell adenocarcinoma are two common variant of urinary bladder cancer. The pathogenesis and histological feature of these four types of bladder cancer are discussed in this section.

3.1 Primary Urinary Bladder Adenocarcinoma

Primary bladder adenocarcinomas typically have a glandular phenotype and usually develop from the urothelium (Grignon et al., 1991). However, several risk factors have been discovered, including endometriosis, persistent irritation, cystocele, and exstrophy of the bladder that may contribute to primary bladder adenocarcinoma (Grignon et al., 1991). Although bladder adenocarcinoma is frequently detected next to intestinal metaplasia and cyststitis glandularis, recent research indicates that these conditions do not raise the likelihood of adenocarcinoma development (Dadhania et al., 2015). Due to late-stage diagnosis, the prognosis for primary bladder adenocarcinoma is often poor (Dadhania et al., 2015).

The histological features of the primary bladder adenocarcinoma can be categorized as:

1) Enteric Pattern: This subtype displays glands that resemble those found in the intestines and are made up of pseudostratified columnar cells that resemble colorectal adenocarcinomas (Grignon et al., 1991).

2) Mucinous Adenocarcinoma: This subtype of cancer is distinguished by a lot of extracellular mucin and tumor cells that float in a mucin pool (Dadhania et al., 2015; Grignon et al., 1991).

3) Signet Ring Cell Adenocarcinoma: This category consists of poorly differentiated, widely infiltrative cells with noticeable intracellular mucin and indented eccentric nuclei (Grignon et al., 1991).

4) Mixed Type: The mixed type corresponds to tumors that exhibit many growth patterns (Dadhania et al., 2015).

5) Not Otherwise Specified (NOS): There are some cases that shows undifferentiated glandular development without a clear pattern, which are categorized as not otherwise specified (Grignon et al., 1991).

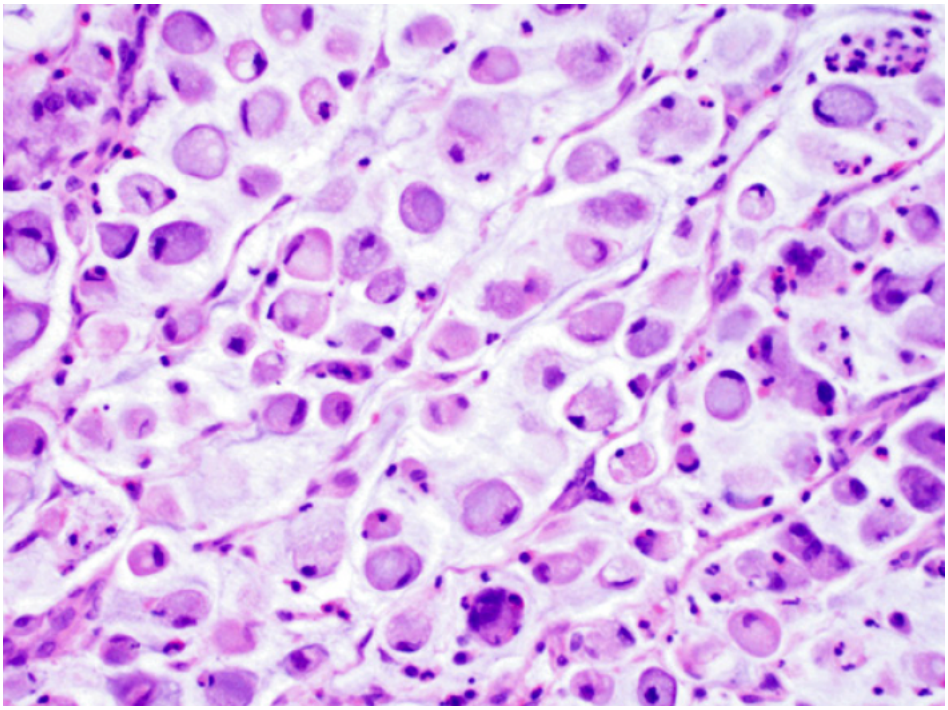

Fig 1: A signet ring cell primary bladder adenocarcinoma with noticeable intracellular mucinandindented eccentric nuclei (Dadhania et al., 2015).

3.2 Secondary Urinary Bladder Adenocarcinoma

The secondary urinary bladder adenocarcinoma usually occurs due to metastasis from other organs, such as the colon, prostate, endometrial, cervix, breast, stomach, and lungs (Bates et al., 2000; Melicow, 1955). The type of bladder cancer occurs due to the spread of the pathologic characteristics through hematogenous or lymphatic pathways or by direct extension (Bates et al., 2000; Grignon et al., 1991). Some examples of secondary bladder adenocarcinoma are as follows:

1) Colorectal Adenocarcinoma: Colorectal adenocarcinomas are often indistinguishable from primary bladder cancer based on morphological characteristics. The tumor cells of the bladder present cytoplasmic and nuclear immunostaining of β-catenin (Dadhania et al., 2015; Roy et al., 2011).

2) Prostatic Adenocarcinoma: The secondary adenocarcinoma that occurs due to the metastasis from prostate have distinguishable dot-like Golgi complex (Dadhania et al., 2015; Roy et al., 2011).
3) Endometrial and Cervical Adenocarcinomas: The endometrial tumors show similar histologic features as primary bladder adenocarcinoma. In contrast, the endocervical tumors show mucin containing columnar cells with complex glandular structure (Dadhania et al., 2015; Bates et al., 2000).
4) Villous Adenoma: Villous adenoma manifests as an exophytic papillary mass that resembles papillary urothelial cancer (Dadhania et al., 2015; Cheng et al., 1999).
5) Adenocarcinoma in situ: In situ adenocarcinomas manifest papillary and glandular shape distinguished by columnar cells (Bates et al., 2000; Chan et al., 2001).
6) Urothelial Carcinoma: Secondary bladder adenocarcinoma my arise from urothelial carcinoma with genuine glandular differentiation (Dadhania et al., 2015).

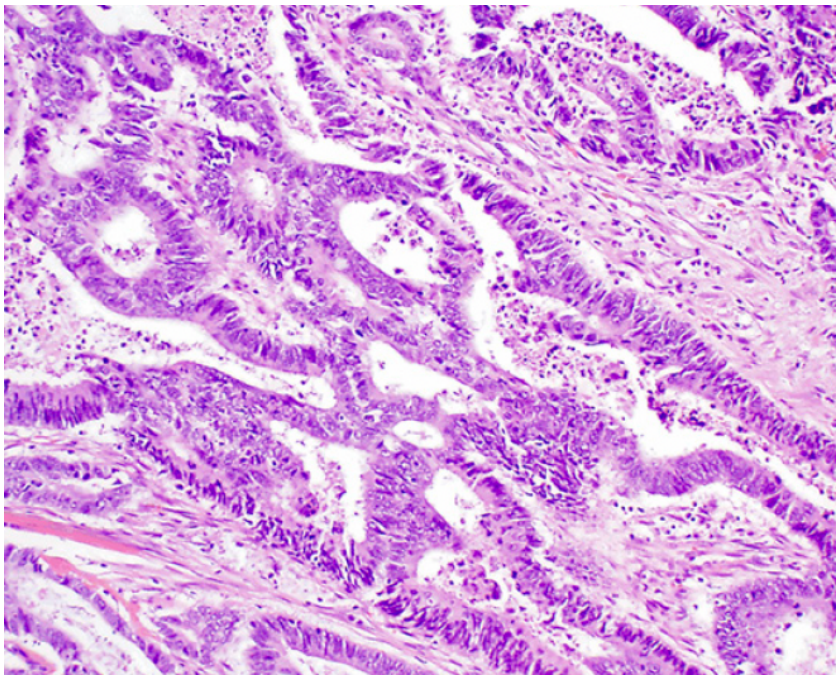

Fig 2: A colorectal secondary urinary bladder adenocarcinoma invading bladder wall (Dadhania et al., 2015).

3.3 Urachal Urinary Bladder Adenocarcinoma

The urachus, a fibrous remnant connecting the bladder to the umbilical cord during development, is the source of urachal adenocarcinoma, a separate subtype of bladder cancer (Grignon et al., 1991). It often displays growth patterns, such as enteric and mucinous patterns, that are comparable to those of primary bladder adenocarcinoma. However, it frequently has more significant glandular differentiation with a well-preserved architecture (Schubert et al., 1982).

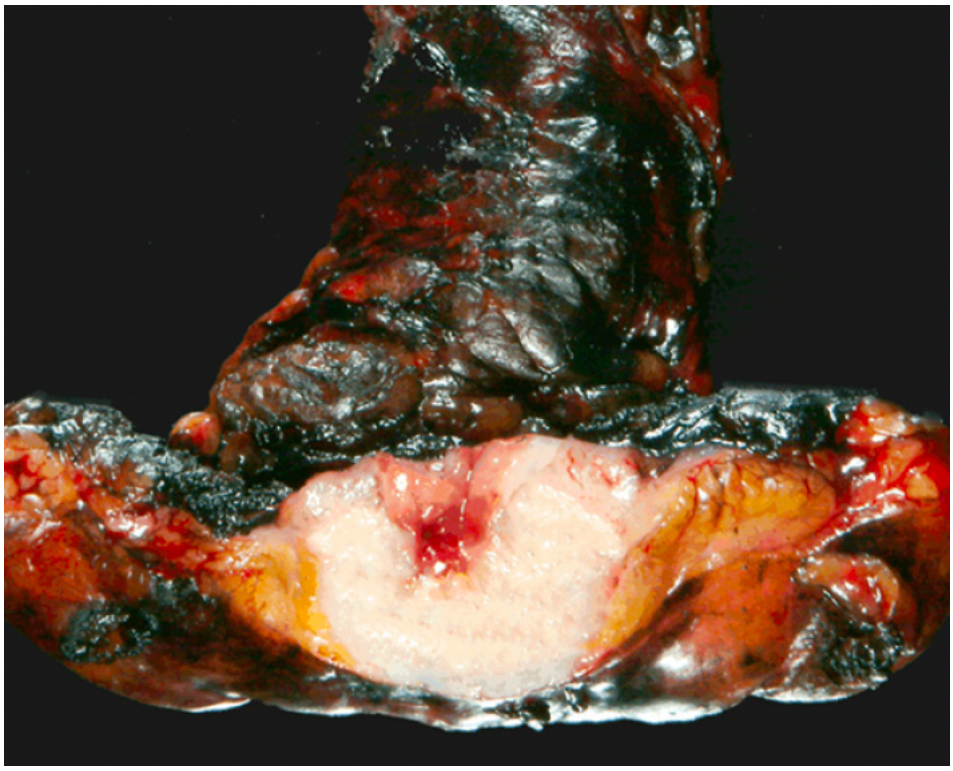

Fig 3: A urachal urinary bladder adenocarcinoma (Dadhania et al., 2015).

3.4. Clear Cell Urinary Bladder Adenocarcinoma

Bladder clear cell adenocarcinoma, another variant of urinary bladder cancer, coexists with endometriosis or müllerianosis and have similar physical characteristics with female genital tract clear cell cancer (Drew et at., 1996). The tumor that causes clear cell urinary bladder adenocarcinoma shows papillary, solid, or turboelectric pattern while observed under a

microscope (Oliva et al., 2002). The nucleoli of the cells are very prominent, and the cytoplasm is transparent or very mildly eosinophilic (Chan et al., 2001). The tumor has also significant amount of hobnail cells (Drew et at., 1996).

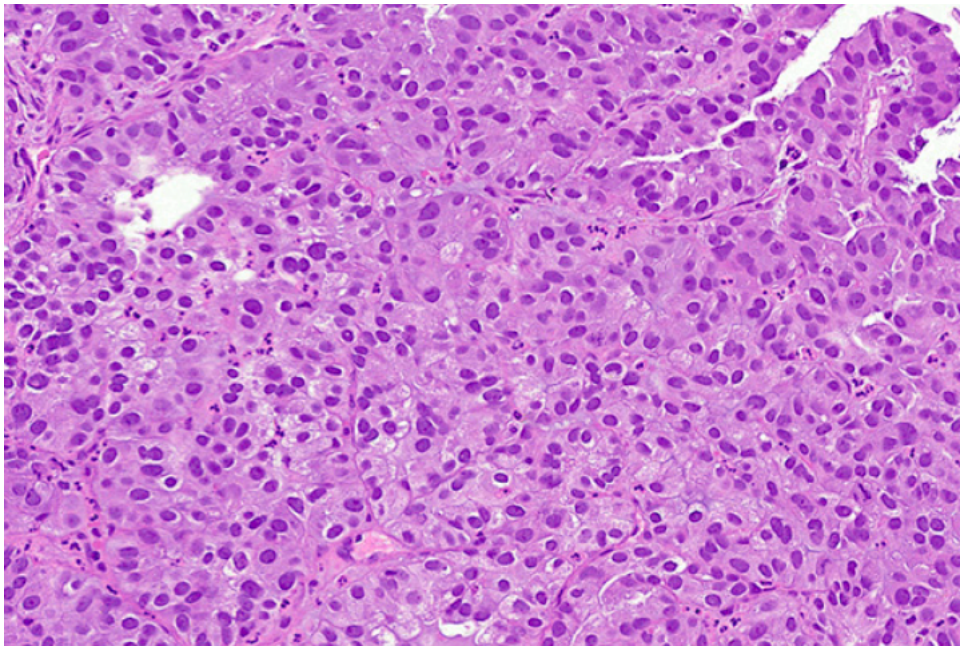

Fig 4: Clear cell urinary bladder cancer showing solid and papillary growth (Dadhania et al., 2015).

Chapter 4

Methodology

In this study, we systematically review the treatment regimens of urinary bladder adenocarcinoma and develop a comparative analysis among different treatment modalities. To do so, we rigorously review the existing literature corresponding to the treatment of bladder cancer. Specifically, we use the PubMed's advance search engine to find related articles. We also used Google Scholar, another tool to search research articles, to find some supplementary articles that has been used in the introduction and other sections. Our comprehensive search results for the treatment of bladder cancer are summarized in the following table.

Authors	Treatment Regimens	Types of Bladder Cancer
Popov et al., 2023	Chemotherapy, Radiotherapy, Cystectomy, BCG vaccine	Secondary adenocarcinoma
Duchesne et al., 2000	Cystectomy and Palliative radiotherapy	Not mentioned
Dadhania et al., 2015	Radical cystectomy, Radiation therapy, Cisplatin-based chemotherapy regimen - MVAC, BCG Vaccine	Primary, secondary, urachal, and clear cell adenocarcinoma
Tsironis et al., 2018	Chemotherapy, Cystectomy, External beam radiotherapy (EBRT)	Primary adenocarcinoma
Vasudevan et al., 2017	Radical/partial cystectomy with pelvic lymph node dissection with or without adjuvant radio/chemotherapy.	Primary adenocarcinoma
Zaghloul et al., 2006	Cystectomy, Radiotherapy	Primary adenocarcinoma
Uhlig et al., 2018	Transurethral resection and Cystectomy with ileum neobladder and Adjuvant radiochemotherapy	Primary adenocarcinoma
Roy et al., 2011	Radical/partial cystectomy with or without Adjuvant radiation	Primary, secondary, urachal, and clear cell adenocarcinoma

Tatli et al., 2015	FOLFOX4 (fluorouracil, leucovorin, oxaliplatin) regimen	Primary adenocarcinoma
Yu et al., 2015	GC plus S-1 Drug regimen, Radical cystectomy	Primary adenocarcinoma
Kim et al., 2018	GP (gemcitabine + cisplatin), MVAC (methotrexate + vinblastine + adriamycin + cisplatin), MVP (methotrexate + vinblastine + cisplatin), FP (5-FU + cisplatin), FOLFOX (oxaliplatin + leucovorin + 5-FU), FAP (5-FU + adriamycin + cisplatin), FEP (5-FU + epirubicine + cisplatin), EP (etoposide + cisplatin)	Primary, and urachal adenocarcinoma
Cormio et al., 2014	Cystectomy and/or chemotherapy, Cisplatin/pemetrexed	Secondary adenocarcinoma
De Santis et al., 2007	Cisplatin-based chemotherapy, i.e., oxaliplatin, vinflunine and pemetrexed and Complete resection	Primary and secondary adenocarcinoma
Pini et al., 2021	Neoadjuvant MVAC chemotherapy	Primary adenocarcinoma
von der Maase et al., 2000	GC plus S-1 drug regimen, MVAC	Primary adenocarcinoma
Sternberg et al., 2006	MVAC	Primary and secondary adenocarcinoma
von der Maase et al., 2005	MVAC	Primary adenocarcinoma
Galsky et al., 2007	TIP	Primary adenocarcinoma
Johnson et al., 1972	GC plus S-1 drug regimen	Primary adenocarcinoma
Hong et al., 2009	VIP, EP, BOMP, FAP and TP	Primary adenocarcinoma
Ploussard et al., 2014	Combination of resection, chemotherapy, and radiotherapy	Primary adenocarcinoma
Grignon et al., 1991	Cystectomy with or without Radiation Therapy, Cystectomy with or without Chemotherapy, Chemotherapy, Radiation Therapy	Primary, secondary, and urachal adenocarcinoma

Table 1: Existing treatment regiments for bladder cancer.

Chapter 5

Treatment Regimens

The treatment regimens of urinary bladder adenocarcinoma can be divided into two main directions. In one direction, various drug-based procedures are used to treat this disease. In the other direction, surgical procedures with or without medications is performed to treat this illness. In the following subsections, drug-based, surgical, and other existing treatment regiments from literature are briefly reviewed.

5.1. Drug-based Treatment Regimens

Drug-based treatment regimens mainly include different drug combinations (Tatli et al., 2015; Yu et al., 2015; Kim et al., 2018; von der Maase et al., 2000; Galsky et al., 2007). These drug-based medications can be categorized as either cisplatin-based or not. The combination of drugs that are used to treat urinary bladder adenocarcinoma is described in the following subsections.

5.1.1. Cisplatin-based Drug Combination

Cisplatin based drug combinations is one of the most used medications that is prescribed for treating urinary bladder adenocarcinoma (Yu et al., 2015; Kim et al., 2018). There are different medication combinations that can be used with chemotherapy that uses cisplatin (von der Maase et al., 2000).

5.1.1.1. GC (Gemcitabine plus Cisplatin) plus S-1

The GC (Gemcitabine plus Cisplatin) plus S-1 is typically used to treat locally advanced primary bladder adenocarcinoma. This combination of drug acts by preventing the growth and replication of cancer cells (Yu et al., 2015).

The GC (Gemcitabine plus Cisplatin) plus S-1 regimen has shown considerable promise as first-line chemotherapy for urothelial, specifically transitional cell carcinoma. According to Yu et al. (2015), this treatment regimen significantly downstaged the tumor and reduced micro metastases for patients with a locally advanced stage. As a result, this significantly reduces complications in surgery (Yu et al., 2015). This trial considers the GC plus S-1 treatment regimen for neoadjuvant chemotherapy in primary adenocarcinomas of the urinary bladder with six patients under treatment. Among these, two of them showed complete response and another two showed partial responses. However, one patient didn't show any significant response and continued with the stable disease. Overall, the adverse effects of the medication were tolerable and managed. This study also indicates that the GC plus S-1 regimen is promising in the management of urinary bladder adenocarcinoma. However, more studies with larger patient populations are required to demonstrate the regimen's efficacy and safety (Yu et al., 2015). In a separate study, Voutsadakis demonstrated that triple targeted therapy improved overall survival (OS) compared to regular chemotherapy (Voutsadakis, 2020).

5.1.1.2. 5-FU (Fluorouracil) and Cisplatin

5-FU (Fluorouracil) is a chemotherapeutic medication that prevents cancer cells from synthesizing DNA and RNA (Kim et al., 2018). On the other hand, cisplatin prevents cancer cells from replicating their DNA (Kim et al., 2018). According to Kim et al. (2018), the FP

regimen, which consists of 5-FUand cisplatin, was effective in treating urinary bladder adenocarcinoma. This study conducts a trial of nine patients with bladder adenocarcinoma. These patients received 5-FU and cisplatin and the response of this treatment regimen is observed. The result of this study indicates a significant response of the patients with these drugs, with a 44.8% overall response rate indicating a considerable tumor response. The median survival of 24.5 months was also like other studies utilizing FP, 5-FU plus cisplatin. The result of this study dictates that this treatment regimen might be a beneficial option for treating urinary bladder adenocarcinoma and act as a ground for further research and clinical practice in this direction (Kim et al., 2018).

5.1.1.3. MVAC (Methotrexate + Vinblastine + Adriamycin + Cisplatin)

MVAC (Methotrexate + Vinblastine + Adriamycin + Cisplatin) is a combination chemotherapy regimen that also includes vinblastine and doxorubicin and adriamycin. This combination of medication has served as a mainstay treatment for a long time for treating urinary bladder adenocarcinoma (von der Maase et al., 2000; Sternberg et al., 2006).

The treatment of urinary bladder adenocarcinoma has showed promising results when using the MVAC medication regimen. In the phase III trial conducted by von der Maase et al. (2000), MVAC and gemcitabine/cisplatin outperformed other combination chemotherapy regimens in terms of longer median survival rates, reaching up to 14.8 months and 13.8 months, respectively, in clinical trials. In a separate randomized phase III trial by Sternberg et al. (2006), high-dose MVAC was given every two weeks and standard-dose MVAC provided every four weeks were contrasted. The trial analyzed the progression-free survival of the patients after 7.3 years of follow-up. The results show a significant increase in the progression-free survival and marginal increase of overall survival due to the high-dose regimen's much higher overall and complete response rates (Sternberg et al., 2006).

Furthermore, the long-term results of the trail, von der Maase et al. (2000), were reported in von der Maase et al. (2005). The long-term results show that the high-dose MVAC arm had a 5-year survival rate of 21.8% whereas the standard-dose arm had a 5-year survival rate of 13.5% (von der Maase et al., 2005).

These results demonstrate the efficacy of the MVAC regimen, especially the high-dose form, in the management of urinary bladder adenocarcinoma. It has shown longer survival times, higher overall response rates, and possibly therapeutic effects. To confirm these findings and establish the most effective application of MVAC in the management of this form of cancer, additional investigation and clinical studies are required.

5.1.1.4. MVP (Methotrexate, Vinblastine, and Cisplatin)

MVP is a combination chemotherapy regimen used to treat bladder adenocarcinoma. This treatment regimen contains cisplatin, methotrexate, and vinblastine. In the trial by Kim et al. (2018), one patient was treated with MVP. After treating the patient with MVM, the disease showed gradual progression trough patient's body. Since, only a single patient was involved in this trial, more study with large population size is required to further characterize the efficacy of this medication regimen.

5.1.1.5. TIP (Paclitaxel, Ifosfamide, and Cisplatin)

TIP is a combination chemotherapy treatment plan that consists of paclitaxel, ifosfamide, and cisplatin. In Kim et al. (2018), the authors tested this treatment plan to see how well it treats bladder adenocarcinoma.

The overall response rate for the treatment of urinary bladder adenocarcinoma with TIP was found to be 36% in a study by Galsky et al. (2007). This shows that the treatment is working, with a sizable percentage of patients showing a decrease in tumor size or stabilization of the

condition. Overall survival was reported to be 24.8%, indicating a moderate long-term survival result for TIP treatment patients. These results suggest that TIP may be an effective treatment for adenocarcinoma of the urinary bladder (Kim et al., 2018).

5.1.1.6. Other Cisplatin Based Drug Regimens

There are some uncommon cisplatin-based drugs reported in literature that have also been used to treat urinary bladder adenocarcinoma. Kim et al. (2018) and Hong et al. (2009) reported some cisplatin-based drugs regimens, including VIP (Etoposide + Ifosfamide + Cisplatin), EP (Etoposide + Cisplatin), BOMP (Bleomycin + Vincristine + Mitomycin + Cisplatin), FAP (5-FU + Adriamycin + Cisplatin), and TP (Paclitaxel + Cisplatin).

These drug combination gives better outcomes in the treatment of urinary bladder adenocarcinoma, as reported by Hong et al. (2009). The research found that the treatment was effective, with a 36% overall response rate being particularly noteworthy. Furthermore, 8% was reported as the observed progression-free survival, indicating a period of disease stability. Amazingly, the total survival rate was 47%, highlighting the fact that a sizeable fraction of patients managed to survive for an extended period despite their illness. These results strongly imply the potential efficacy of these medication regimens as effective therapy choices for urinary bladder adenocarcinoma (Kim et al., 2018).

5.1.2. Non-cisplatin-based Drug Combination

Even though cisplatin-based drug regiments are mostly prescribed for bladder cancer, non-cisplatin-based medication regimens are not uncommon. Some non-cisplatin-based treatment regimens are briefly described in the following subsections.

5.1.2.1. FOLFOX4 (Fluorouracil, Leucovorin, Oxaliplatin)

FOLFOX4 is another medication regimen and more recent chemotherapy that has been investigated in the first- or second-line settings for urinary bladder adenocarcinoma. The chemotherapy treatment FOLFOX4 consists of the drugs fluorouracil (5-FU), leucovorin, and oxaliplatin.

According to case reports and research, the chemotherapy regimen FOLFOX4 (5-fluorouracil, leucovorin, oxaliplatin) has shown encouraging results for urinary bladder adenocarcinoma (Tatli et al., 2015). These studies also reported that complete responses to FOLFOX4 chemotherapy have been attained in several case reports, more specifically at the conclusion of the sixth month of treatment.

Other case reports are also available in Teo et al. (2011). These results imply that FOLFOX4 may be a more effective chemotherapy regimen for the management of urinary bladder adenocarcinoma.

5.1.2.2. TC (Paclitaxel + Carboplatin) and VI (Etoposide + Ifosfamide)

In the treatment of urinary bladder adenocarcinoma, the combination medication regimens TC and VI have demonstrated good results (Kim et al., 2018).

Both regimens showed an overall response rate of 36%, indicating a favorable therapeutic response, according to a study by Hong et al. (2009). In 8 out of 14 patients, the progression-free survival was noted, suggesting a time during which the disease did not advance. A sizable fraction of patients survived during the research, as indicated by the reported overall survival rate of 47%.

These results imply the viability of TC and VI regimens as curative treatments for urinary bladder cancer. To validate these findings and maximize their application in treating this uncommon cancer, more investigation and clinical investigations are required (Kim et al., 2018).

The relative comparison among different drug combination is summarized in the following table:

Drug Combination	No. of Patients	Overall Response Rate (ORR) (%)	Progression Free Survival (PFS) (months)	Overall Survival (OS) (months)	Outcomes	Authors	Types of Bladder Cancer
GC (Gemcitabine + Cisplatin)	203	49.4	7.4	13.8	Effective as a first-line chemotherapy with fewer side effects	Von der Masse et al., 2000	Primary urothelial (transitional) cell carcinoma
	203	Not reported	7.7	14	Effective as a first-line chemotherapy with fewer side effects	von der Masse et al., 2005	Primary urothelial (transitional) cell carcinoma
	5	40	14.3	23.5	More assessment required	Kim et al., 2018	Urachal and nonurachal bladder adenocarcinoma
GC plus S-1	6	66.67	Not reported	Not reported	PFS and OS also need to be considered	Yu et al., 2015	Urachal and Primary adenocarcinoma

Cisplatin	120	11	2.4	8.2	Not much effective	Loehrer et al., 1992	Primary and Secondary urothelial carcinoma
MVAC (Methotrexate + Vinblastine + Adriamycin + Cisplatin)	202	45.7	7.4	14.8	Higher overall survival rate and comparable overall response rates, successful in treating bladder cancer	Von der Masse et al., 2000	Primary urothelial (transitional) cell carcinoma
	202	Not reported	8.3	15.2	Higher overall survival rate and comparable overall response rates	Von der Masse et al., 2005	Primary urothelial (transitional) cell carcinoma
	129	58	8	14.9	Show promise as an effective drug	Sternberg et al., 2006	Primary urothelial (transitional) cell carcinoma
	126	38	6.6	12.5	Potential for effective chemotherapy	Loehrer et al., 1992	Primary and Secondary urothelial carcinoma
	3	66.67	14.3	23.5	Need further analysis	Kim et al., 2018	Urachal and nonurachal bladder adenocarcinoma
HD (High Dose) - MVAC	134	72	9.5	15.1	Higher dose shows more efficacy	Sternberg et al., 2006	Primary urothelial (transitional) cell carcinoma

5-FU (Fluorouracil) plus Cisplatin (FP)	7	42.86%	10.1	16.3	Beneficial for treating urinary bladder adenocarcinoma	Kim et al., 2018	Urachal and nonurachal bladder adenocarcinoma
MVP (Methotrexate, Vinblastine, and Cisplatin)	1	0	14.3	23.5	Additional research required to characterize effectiveness	Kim et al., 2018	Urachal and nonurachal bladder adenocarcinoma
TIP (Paclitaxel, Ifosfamide, and Cisplatin)	11	36	Not reported	24.8	Potentially successful therapy for adenocarcinoma of the urinary bladder	Galsky et al., 2007	Primary bladder adenocarcinoma
Other cisplatin-based: VIP, EP, BOMP, FAP, and TP	14	36	8	47	Possibility of effectiveness as treatment of urinary bladder adenocarcinoma	Hong et al., 2009; Kim et al., 2018	Primary, Secondary and urachal adenocarcinoma
FOLFOX (Fluorouracil, Leucovorin, Oxaliplatin)	1	100	10.1	16.3	Potentially effective chemotherapy for the urinary bladder adenocarcinoma	Kim et al., 2018	Urachal and nonurachal bladder adenocarcinoma
Other noncisplatin-based: TC, VI	14	36	8 months	47 months	Treatment options for urinary bladder adenocarcinoma	Hong et al., 2009, Kim et al., 2018	Primary and secondary adenocarcinoma

Table 2: Relative comparison of drug combinations of bladder cancer.

5.2. Surgical Treatment Regimens

Urinary bladder adenocarcinoma is also treated with surgical procedures to remove the cancerous cells from the urinary bladder. Most often, surgery of the bladder is performed along with some cancer medication or radiation therapy to mitigate future progression (Uhlig et al., 2018; Grignon et al., 1991). Some common surgical treatment plans for the urinary bladder adenocarcinoma are presented in the following subsections.

5.2.1. Cystectomy

Cystectomy is a surgical procedure that corresponds to the removal of urinary bladder. Radical cystectomy with or without node dissection is the recommended surgical approach for most patients with primary bladder adenocarcinoma. This is the most effective method of treating bladder-specific localized transitional cell carcinoma (TCC), which entails the removal of the whole bladder as well as any adjacent lymph nodes. However, cystectomy alone may not be effective treatment plan for urinary bladder adenocarcinoma (Uhlig et al., 2018; Zaghloul et al., 2006, Vasudevan et al., 2017).

5.2.2. Surgery and Radiation Therapy

In most of the cases surgery alone cannot completely remove cancerous cells of the urinary bladder. Hence, surgery is frequently used in addition to adjuvant radiation for achieving total tumor excision (Grignon et al., 1991). According to Zaghloul et al. (2006), postoperative radiation has shown to increase disease-free survival and local control in patients with urinary bladder adenocarcinoma.

5.2.3. Surgery and Chemotherapy

Chemotherapy is often prescribed before surgery with late-stage urinary bladder adenocarcinoma. The chemotherapy localizes the cancer cells and makes the surgery more effective for cancerous cell removal as per Grignon D.J. et al. (1991). In Bamias et al. (2005), the authors found that neoadjuvant chemotherapy has demonstrated effectiveness in enhancing outcomes when given before ultimate surgical procedure.

5.2.4. Surgery and Radiochemotherapy

In some cases of urinary bladder adenocarcinoma treatment, surgery is accompanied by both radiotherapy and chemotherapy. Precisely, transurethral resection and cystectomy with ileum neobladder followed by adjuvant radiochemotherapy have been used to treat primary bladder adenocarcinoma. The goal of this treatment plan is to control the oncological characteristics while maintaining the quality of life according to Uhlig et al. (2018).

5.3. Other Treatment Plans

There exist some uncommon treatment plans in literature to treat bladder cancer which are briefly presented in the following subsections.

5.3.1. Combination Chemoradiotherapy

Generally, radiation therapy or chemotherapy alone is not the preferred treatment option and is typically viewed as inferior to radical cystectomy for individuals with urinary bladder adenocarcinoma as per Shelley et al. (1996). However, chemoradiation therapy can be used as a drastic treatment alternative to achieve local disease control in circumstances where patients are not candidates for surgery or reject cystectomy. External beam radiation therapy (EBRT) and chemotherapy combined has shown better results according to the study of

Ploussard et al. (2014). Furthermore, combination chemoradiotherapy may be a good option for people who are unable or reluctant to have a cystectomy.

5.3.2. BCG Vaccine

In studies led by Dadhania et al. (2015) and Popov et al. (2023), BCG vaccine has been used as a treatment plan for urinary bladder adenocarcinoma. In these studies, it has been shown that BCG vaccine may be effective in some cases of urinary bladder adenocarcinoma. However, some individuals may not respond to the intravenous BCG vaccine dosage as per these researchers.

Chapter 6

Discussion

In this section, we develop a comparative analysis among different treatment regimens of bladder adenocarcinoma. Specifically, this discussion primarily focuses on analyzing the effects of these drug-based treatment plans on the survival and response rates of patients with disease. Further, we develop an analysis based on the effects of different treatment regimens on different types of balder cancer.

First, we develop a comparative analysis among different cisplatin-based drug regimens that has been discussed in this thesis. Among these drug combinations, GC plus S-1 has the highest overall response rate (49%) (Yu et al., 2015; von der Maase et al., 2000; Johnson et al., 1972). However, the overall survival of MVAC and other cisplatin-based drugs (47 months) is greater than the overall survival of GC plus S-1 (13.8 months for standard dose, 14.8 months for high dose) (Yu et al., 2015; von der Maase et al., 2000; Sternberg et al., 2006; von der Maase et al., 2005). The progression free survival (PFS) for both MVAC and other cisplatin-based drugs is 8 months (von der Maase et al., 2000; Sternberg et al., 2006; Hong et al., 2009). Since, the PFS for GC plus S-1 has not been reported by the researchers, comparison in terms of PFS is not possible. On the other hand, 5-FU plus Cisplatin, MVP, and TIP have survival rate of 44.8%, 44.8%, and 36% respectively (Kim et al., 2018; Galsky et al., 2007). The overall survival of these drugs is reported as 24.5 months (5-FU plus Cisplatin and MVP) and 24.8 months (TIP), which indicates that these drug combinations are moderately effective in treating urinary bladder adenocarcinoma (Kim et al., 2018; Galsky et al., 2007). Based on this data, GC (Gemcitabine plus Cisplatin) with S-1 outperforms all

other cisplatin-based drug regiments. Moreover, the clinical trial of GC plus S-1 has the largest the population size, which makes the results of the trial more plausible.

Second, we compare the non-cisplatin-based drug combinations that has been introduced in this study. We find that FOLFOX4 outperforms TC and VI in terms of overall response rate (48.8% for FOLFOX4 and 36% for TC and VI) and PFS (10.6 and 8 months respectively) (Kim et al., 2018; Hong et al., 2009). However, the overall survival rate of TC and VI (47 months) is higher than FOLFOX4 (24.5 months) (Kim et al., 2018; Hong et al., 2009). Overall, both can be used as a potential treatment option for urinary bladder adenocarcinoma.

Third, we compare among cisplatin-based and non-cisplatin-based drug combinations for treating urinary bladder adenocarcinoma. Based on the data presented before, it turns out that the cisplatin-based drug combinations outperform non-cisplatin-based drugs in terms of overall response rate (49% for GC plus S-1 and 48.8% for FOLFOX4). The TC and VI, a non-cisplatin-based drug combination has the comparable overall survival as MVAC, a cisplatin-based drug combination. Moreover, the PFS of FOLFOX4 MVP is same (10.6 months), which is also highest for all the drug combinations compared. However, the population size (29 for FOLFOX4 and 14 for TC and VI) of these trials are small compared to GC plus S-1 (229). Hence, non-cisplatin-based drugs can be further researched with higher population size.

Finally, we analyze the effect of treatment regimens on different types of cancers. Most of the treatment regiments has been used for treating primary bladder adenocarcinoma. Specifically, the GC plus S-1, 5-FU and cisplatin, MVAC, MVP, TIP, FOLFOX4, TC and VI, and other cisplatin-based drug combination - VIP, EP, BOMP, FAP, and TP has been used to treat primary bladder adenocarcinoma. Among them, the GC plus S-1 regimen is most effective in terms of overall response rate (49%) for treating primary bladder adenocarcinoma (see table

2). On the other hand, MVAC, TC and VI, and other cisplatin-based drug combination - VIP, EP, BOMP, FAP are equally effective in terms of overall survival length (47 months). However, MVP and FOLFOX4 regimen outperforms MVAC, TC and VI, and other cisplatin-based drug combinations in terms of progression free survival (10.6 months). The 5-FU and cisplatin has also been used to treat urachal urinary bladder adenocarcinoma besides primary bladder adenocarcinoma. This regimen has shown better response in treating primary bladder adenocarcinoma compared to urachal adenocarcinoma (Kim et al., 2018). For the treatment of secondary bladder adenocarcinoma, MVAC, and TC and VI has been used. Among them, MVAC has shown better overall survival (47 months), though the overall response rate of them is equal (36%). Based on this analysis, it's evident that cisplatin-based drug combinations can be recommended for treating most types of bladder cancer.

On the other hand, surgery-based treatment methods are also being popular for treating urinary balder adenocarcinoma. The most common surgical method is cystectomy, the removal of urinary bladder (Uhlig et al., 2018). However, in most cases cystectomy alone is not effective. Hence, surgery of the tumor is accompanied with chemotherapy, radiation therapy and radiochemotherapy (Uhlig et al., 2018; Grignon et al., 1991). These type of treatment plans has proved to be more effective than surgery alone. There are some other nontrivial treatment plans such as combination chemotherapy and BCG vaccine, which has also shown promise in some cases (Popov et al., 2023; Ploussard et al., 2014).

Chapter 7

Conclusion

This dissertation addressees the effects of several drug-based therapy regimens on patients with urinary bladder adenocarcinoma in terms of survival and response rates through a methodical assessment of related research and analysis of the available data. A major outcome of our analysis is that cisplatin-based drugs show significant efficacy in treating urinary bladder adenocarcinoma. Moreover, we find that composite treatment plans, i.e., both surgery and medication, may show significant response in patient management which needs to be justified by further research and data. The results of this investigation have significant ramifications which immediately leads to many important future research directions. In one direction, well-designed clinical trials and combination medicines can be pursued for better drug development purposes. In a separate track, understanding resistance mechanisms and biomarker identification can also be explored to develop early detection and treatment. In the future, we plan to continue these lines of research to further, focusing on developing effective treatment and patient management plans for urinary bladder adenocarcinoma.

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