Kenar D. Jhaveri
Abdulla K. Salahudeen
Editors

Onconephrology

Cancer, Chemotherapy and the Kidney

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Editors
Kenar D. Jhaveri, MD
Department of Medicine, Division of Kidney Diseases and Hypertension
North Shore University Hospital and Long Island Jewish Medical Center
Hofstra North Shore LIJ School of Medicine
Great Neck
New York
USA

Abdulla K. Salahudeen, MD, MBA, FRCP
Nephrology Section, General Internal Medicine
University of Texas MD Anderson Cancer Center
Houston
Texas
USA

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Foreword

We all recognize that major advances have been made in the treatment of patients with leukemia, lymphoma, breast cancer, prostate cancer, colon cancer, and several other malignancies over the past few decades. As a consequence, the number of survivors after a cancer diagnosis has increased from 3 million in 1971 to about 14.5 million today, which experts attribute to advancements in diagnosis, treatment, and supportive care.

The field of hematology–oncology has exponentially grown to include rationally designed biologics and small molecules that target dysregulated pathways. Though the use of these new agents has led to remarkable improvement in overall survival, some of these drugs cause nephrotoxicity. More importantly, since cancer is primarily a disease affecting older people, the renal function of patients at the time of diagnosis may be compromised due to expected decline in renal function attributed to aging cells. Given that up to a quarter of patients with a cancer diagnosis will develop new onset renal impairment, a new discipline that aims to understand and manage the challenging overlapping fields of nephrology and oncology is needed. The recent acknowledgment of the field of "Onconephrology" was heralded by the creation of the Onconephrology Forum (ONF) by American Society of Nephrology (ASN) in 2010 and the Cancer & the Kidney International Network (c-kin.org) in 2014. The publication of this textbook by Jhaveri et al., "Onconephrology: Cancer, Chemotherapy and the Kidney: A Case-Based Approach" is therefore timely and necessary. The rising awareness of this nascent scientific field will hopefully lead to improved patient outcomes.

Acute kidney injury in patients with cancer may occur by at least two mechanisms: it could arise as a complication of a particular cancer treatment (e.g., tumor lysis syndrome, drug-induced nephropathy, posttransplant related kidney diseases, surgical procedures) or be related to the neoplasm itself (e.g., renal cell cancer, anatomic obstruction due to a metastatic lesion or obstructing mass, or myeloma/amyloid affecting the kidney). It is a fact that a cancer patient that harbors or develops a kidney dysfunction has a worse prognosis than one without renal impairment.

Education about onconephrology is of utmost importance so that a true multidisciplinary approach can be developed. A growing number of treatment centers and patient support groups have started to offer onconephrology-based care programs.

More information and resources are urgently needed to help our patients understand their condition and to enhance their chances at survival.

North Shore -LIJ Cancer Institute and
Hofstra North Shore -LIJ School of Medicine,
New York, USA

Jacqueline C. Barrientos, MD
Kanti R. Rai, MD

Preface

I am grateful and fortunate to have had great opportunities, family and friends, teachers and mentors. I graduated from Trivandrum Medical School in state of Kerala, south of India and had my initial clinical and research training in the early 80s at University of Newcastle upon Tyne under Professors David Kerr and Robert Wilkinson. My second set of clinical and research training—this time included laboratory research—was at the University of Minnesota under professors Thomas Hostetter and Karl Nath. I had an opportunity to hone my skills and establish myself as a researcher, teacher, and a clinician in the 90s while working under Professor John Bower at the University of Mississippi Medical Center. In 2006, I moved to University of Texas MD Anderson Cancer Center as the chief of nephrology section that had given me the opportunity to set up the first formal nephrology section dedicated to address the nephrology problems in cancer patients. It became immediately clear to me that most of the nephrological problems in cancer patients are unique and severe. This led me to form the first onconephrology forum of nephrologists in the USA taking care of cancer patients, which with the support of the president of ASN, professor Joseph Bonventre of Harvard Medical School became formally the ONF of ASN in 2011. This also was an opportune time in that I met in our first meeting the corresponding editor of this book, Dr. Kenar Jhaveri MD, associate professor at Hofstra North Shore–LIJ School of Medicine, trained at Memorial Sloan Kettering Cancer Hospital in cancer-related nephrology, who was equally enthusiastic and certain about the future of onconephrology. Indeed, onconephrology has become a burgeoning area in nephrology—a fertile area for learning, training, research, and improved patient care. Thanks to many nephrologists and scientists who have contributed and continued to contribute to the growth of onconephrology.

Abdulla K. Salahudeen MD, MBA, FRCP

Acknowledgments

To our trainees and patients, from whom we have gained knowledge.

To our gurus and teachers, from whom we have gained wisdom.

To our colleagues, from whom we have gained support.

To our family members, who inspire and support us for doing such contributions.

Introduction

Onconephrology: Caring for the Cancer Patient with Kidney Disease

Cancer is one of the leading causes of death and is rapidly becoming a global pandemic. Cancer patients with kidney disease have a worse prognosis with higher mortality and morbidity. The emergence of onconephrology represents a field dedicated to understanding and treating the complex renal problems that arise in cancer patients. The ASN created an ONF in 2010, setting the stage for the growth and development in this new subspecialty. Major cancer centers in the USA have started onconephrology fellowships as part of nephrology training.

A nephrologist who works closely with a hematologist and an oncologist to take care of patients with cancer is called an onconephrologist.

Acute and chronic renal insufficiency is highly prevalent in patients with cancer. Much has to be learnt on preventing acute kidney injury in the cancer patients. Chronic kidney disease and cancer are connected in several ways. Not only cancer can lead to the development of chronic kidney disease and end-stage kidney disease, but also, presence of chronic kidney disease has its associations with cancer. In this book, *Olabisi et al.* explore the causes of acute kidney injury in the cancer patients while *Sachdeva et al*. summarize the link between chronic kidney disease and cancer. In addition, there is an in depth discussion on how to manage anemia, bone disease, and hypertension in chronic kidney disease in cancer patients.

Onconephrology encompasses both the hematologic and solid cancers and their treatment-related complications that affect the kidney. Unlike general nephrology, there are several aspects of onconephrology that are unique. Onconephrology represents a milestone in the history of nephrology: A change in our nephrological perspectives.

The spectrum of fluid and electrolyte disorders in oncology patients has some important and distinct features when compared to those of the general population. *Latcha* embraces a review of all electrolyte disorders one would encounter in a cancer patient and *Gilbert et al*. explore in depth the diagnosis and management of tumor lysis syndrome. In addition, several cancers have been associated with various

glomerular diseases. *Shah* discusses that membranous nephropathy remains the most common glomerular pathology reported in patients with solid tumors. Several reports and studies in the literature suggest that treating the cancer leads to resolution of the glomerular disease.

Chemotherapeutic agents are extremely important in the treatment of malignant diseases. However, they have several side effects including nephrotoxicity which can have drastic effects on patient's morbidity and mortality. Dosing of these agents is essential in chronic kidney disease and end-stage renal disease. *Valika et al*. and *Olyaei et al*. discuss these two very important topics. Targeted therapies have emerged as excellent chemotherapy agents for many different cancers. These drugs are both specific and highly potent. Renal toxicities are now a well-recognized consequence of these therapies. *Humphreys* in his chapter explains that the renal toxicities are often cumulative, and high dose or prolonged therapy increases the risk of renal dysfunction. New drugs continue to be introduced in the market and one has to remain vigilant of their toxicities.

There is lot to be learnt from kidney diseases in cancer patients. From electrolyte disorders, tumor lysis syndrome, acute paraneoplastic glomerular diseases, radiation nephropathy, and others, there is a vast amount of clinical expertise and information that is critical to understand. In addition, it is a part of nephrology that has been lagging behind in research.

Hematopoietic stem cell transplant (HSCT) is the only cure for certain oncologic diseases. HSCT-related kidney complications remain leading cause for significant morbidity and mortality in this population. *Wanchoo et al*. tell us that the various renal toxicities following HSCT are important for the hematologist and nephrologist to understand. In addition, a separate chapter has been dedicated to radiation nephropathy by *Glezerman*.

Over the past decade, laboratory testing for monoclonal protein has improved, so has our understanding of the relationship between monoclonal gammopathies and renal diseases. *Leung et al*. expresses that from monoclonal gammopathy of undetermined significance (MGUS) to myeloma, all spectrum of plasma cell dyscrasias have been associated with renal disease. Confirming the association of kidney disease with monoclonal gammopathy is essential and treatment is geared toward elimination of the clone. Amyloidoses represent a heterogeneous group of diseases which are characterized by deposition of a pathologic proteinaceous substance in the extracellular space in various tissues of the body. The kidney is frequently affected in AL, AA, and several of the hereditary amyloidoses. *Hayes et al*. discuss the new advances in diagnosis of these entities and the treatment that has led to improvement in patient care in the past decade.

Awareness of cancer and the kidney dates back to 2005 when Eric Cohen published the first ever textbook on cancer and the kidney. Most recently, a Cancer and the Kidney International Network (C-KIN) was created in 2014 to improve patient care through better knowledge and awareness on cancer and the kidney related issues.

As nephrologists, we often are not aware of the extent of knowledge and research in the field of uro-oncology. *Salami et al*. and *Rosner* provide an in-depth review on medical and surgical management of renal cell cancer and chronic kidney disease

following nephrectomies respectively. *Abudayyeh* introduces us to the obstructive uropathy that is seen with many cancers. *Sathyan et al*. discuss a thorough review on kidney transplantation related cancers. Finally, *Soni et al*. discuss the role of palliative care in a patient with cancer and renal disease. This is an important and emerging topic of extreme importance to the onconephrologist.

It is in this backdrop, we edit this textbook on onconephrology with chapters written mostly by nephrologists or hematologist/oncologists practicing medicine and nephrology in cancer patients. Some of the topics are well-known, whereas others are less often discussed among nephrologists. In this book, we take a case-based approach to the field of onconephrology. Most of the chapters are written in an easy-to-read style with references to the latest publications in onconephrology topics. We hope this textbook would function as a stimulus or a springboard for both beginners as well as veterans in the field of onconephrology. The case-based discussion of board exam type questions challenges the reader in the subject matter. We are wishing the very best for the burgeoning field of onconephrology. Together, we dedicate this book to all the patients who suffer from both cancer and kidney disease: a devastating combination.

Kenar D. Jhaveri, MD
Abdulla K. Salahudeen, MD, MBA, FRCP

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About the Editors

Kenar D. Jhaveri MD is an associate professor of medicine in the Division of Kidney Diseases and Hypertension at the Hofstra North Shore-LIJ School of Medicine in New York. He is an attending physician at the North Shore University Hospital and Long Island Jewish Medical Center, both in New York. He is the core faculty member of the medical school and the Department of Internal Medicine. Dr. Jhaveri's clinical interests are in taking care of patients with renal complications following bone marrow transplantation and chemotherapy (onconephrology). He is one of the founding members of ASN's workgroup on onconephrology. His inspiration for onconephrology comes from his mentor and guru, Dr. Carlos Flombaum, onconephrologist from Memorial Sloan Kettering Cancer Center. His publications in onconephrology are related to glomerular diseases seen in cancer and chemotherapy, novel chemotherapy agents and nephrotoxicities and renal manifestations of myeloma. He is a columnist for the ASN Kidney News for the section called "Detective Nephron." His interest in nephrology education is vested in using creative ways of teaching nephrology to the medical students, residents, and fellows. He has also published on using social media, and other innovative tools (games, concept maps, role playing, and creative writing) to make nephrology a fun and exciting field. He has conducted numerous faculty development seminars locally to teach these techniques. He continues to have interest in novel ways of sharing information that can make an impact on all fronts: physicians, allied health staff, and the patients. He is a fellow of American Society of Nephrology, American College of Physicians, and National Kidney Foundation. He has a teaching oriented blog called Nephron Power (www.nephronpower.com) and is the Web editor for the official blog of the *American Journal of Kidney Diseases* (*AJKD*), (www.eajkd.org).

Abdulla K. Salahudeen MD, MBA, FRCP joined the Nephrology Department at the University of Minnesota in 1988 as a fellow. He has been in the academic medicine since then moving up to a full tenured professor about 15 years ago when he was at the University of Mississippi Medical Center. He maintained active research both at bench and clinical levels funded through extramural sources that included several national institutes of health (NIH) funding including an RO1 for his seminal work on the mechanism of kidney injury during cold storage. He joined the University

of Texas MD Anderson Cancer Center as the chief of nephrology in 2006 and successfully set up a new section and championed at the national level onconephrology as new and exciting subspecialty in nephrology. He was also the founding chair for the Onconephrology Forum of the American Society of Nephrology. Again, at the national level, he was the president of American Federation of Medical Research (AFMR) in 2011. He has published well over 100 peer reviewed papers, written several chapters in onconephrology.

Contributors

Maen Abdelrahim Division of Medical Oncology, Duke University Medical Center, Durham, NC, USA

Ala Abudayyeh Division of Internal Medicine, Section of Nephrology, University of Texas-MD Anderson Cancer Center, Houston, TX, USA

Madhu Bhaskaran Medicine, Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY, USA

Joseph V. Bonventre Internal Medicine, Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Thomas P. Bradley Medicine, Division of Hematology-Oncology, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY, USA

Craig E. Devoe Medicine, Division of Hematology-Oncology, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY, USA

Michael Esposito Pathology and Laboratory Medicine, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY, USA

Scott J. Gilbert Division of Nephrology, Tufts University School of Medicine, Boston, MA, USA

Ilya G. Glezerman Dept. of Medicine, Renal Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

Christi A. Hayes Medicine, Division of Hematology-Oncology, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY, USA

Benjamin D. Humphreys Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Alla Keyzner Medicine, Division of Hematology-Oncology, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY, USA

Amit Lahoti Section of Nephrology, Department of Emergency Medicine, UT MD Anderson Cancer Center, Houston, TX, USA

Albert Q. Lam Department of Medicine, Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Sheron Latcha Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Edgar V. Lerma Section of Nephrology, University of Illinois at Chicago College of Medicine-Advocate Christ Medical Center, Berwyn, IL, USA

Nelson Leung Department of Nephrology and Hypertension, Hematology, Mayo Clinic Rochester, Rochester, MN, USA

Anna Mathew Medicine, Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY, USA

Vinay Nair Nephrology and Recanati Miller Transplant Institute, Mount Sinai Hospital, Ichan Mt Sinai School of Medicine, New York, NY, USA

Samih H. Nasr Division of Anatomic Pathology, Mayo Clinic Rochester, MN, USA

Opeyemi Olabisi Medicine, Massachusetts General Hospital and Brigham and Women's Hospital, Boston, MA, USA

Ali J. Olyaei Medicine/Pharmacy Practice, OSU/OHSU, Portland, OR, USA

Mitchell H. Rosner University of Virginia Health System, Charlottesville, VA, USA

Mala Sachdeva Medicine, Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY, USA

Simpa S. Salami The Arthur Smith Institute for Urology, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, New Hyde Park, NY, USA

Sharad Sathyan Nephrology and Recanati Miller Transplant Institute, Mount Sinai Hospital, Ichan Mt Sinai School of Medicine, New York, NY, USA

Jane O. Schell Department of Internal Medicine, Section of Palliative Care and Medical Ethics, Renal-Electrolyte Division, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Hitesh H. Shah Medicine, Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY, USA

Anushree Shirali Section of Nephrology, Yale University School of Medicine, New Haven, CT, USA

Ritu K. Soni Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Matthew A. Sparks Division of Nephrology, Department of Medicine, Duke University and Durham VA Medical Centers, Durham, NC, USA

Sascha A. Tuchman Division of Hematological Malignancies and Cellular Therapy, Duke Cancer Institute, Durham, NC, USA

Aziz K. Valika Section of Nephrology, Yale University School of Medicine, New Haven, CT, USA

Manish A. Vira Smith Institute for Urology, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY, USA

Rimda Wanchoo Medicine, Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY, USA

Seth Wright Division of Nephrology, Tufts University School of Medicine, Boston, MA, USA

Chapter 1
Acute Kidney Injury in Cancer Patients

Opeyemi Olabisi and Joseph V. Bonventre

List of Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CNI	Calcineurin inhibitors
ESKD	End-stage kidney disease
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
HSOS	Hepatic sinusoidal obstructive syndrome
ICU	Intensive care unit
KDIGO	Kidney disease improving global outcomes
LIK	Lymphomatous kidney infiltration
MGUS	Monoclonal gammopathy of undetermined significance
MGRS	Monoclonal gammopathy of renal significance
MM	Multiple myeloma
MPGN	Membranoproliferative glomerulonephritis
mTOR	Mammalian target of rapamycin
NSAID	Nonsteroidal anti-inflammatory drugs

O. Olabisi (✉)
Medicine, Massachusetts General Hospital and Brigham and Women's Hospital,
55 Fruit Street, Boston, MA 02114, USA
e-mail: oolabisi@partners.org

J. V. Bonventre
Internal Medicine, Renal Division, Brigham and Women's Hospital,
Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
e-mail: joseph_bonventre@hms.harvard.edu

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RIFLE	Risk, injury, failure, loss, end-stage renal disease
TLS	Tumor lysis syndrome
TMA	Thrombotic microangiopathy
TTP/HUS	Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
VOD	Veno-occlusive disease

There are over 13 million patients who live with or had a history of cancer in 2010 in the USA [1]. While the overall incidence of AKI among this vulnerable group remains unknown, data from several sources suggest that it is quite high and its impact on morbidity, mortality, and cost of care is quite substantial. A Danish population-based study of 1.2 million cancer patients showed 1 and 5 year risk for AKI of 18 and 27 %, respectively [2]. On the other hand, analysis of recent data from 3558 patients admitted over a 3-month period to the comprehensive cancer center at University of Texas M.D. Anderson, Houston, Texas reported an AKI rate of 12 % of which 45 %, arguably preventable, occurred during the first 2 days of admission [3]. Studies conducted in cancer patients in the intensive care unit (ICU) by the same group showed that patients with AKI were more likely to have diminished 60 day survival, as low as 14 % (OR 14.3), and increased associated hospitalization cost by as much as 21 % [4].

Cancer is associated with many risk factors for AKI. Patients with cancer can be debilitated and may be predisposed to hemodynamic compromise associated with total or effective volume compromise. The underlying cancer itself can involve the kidney, and hence, predispose or directly cause kidney injury. Many chemotherapeutic agents can cause AKI. Additionally, AKI impacts the dosing of some chemotherapeutic agents, necessitating adjustment for diminished renal clearance. Patients with cancer who develop AKI are more likely to receive suboptimal dosing of chemotherapy [5]. Therefore, with the emergence of potent and more aggressive chemotherapeutic protocols, many of which are now accessible to previously excluded elderly patients with cancer, medical management of kidney health in cancer patients has become more complicated, and necessarily, more multidisciplinary.

This chapter reviews the epidemiology of AKI in cancer patients. The challenging issues about timely diagnosis and management are also discussed. Topics such as tumor lysis syndrome, hyponatremia, and other electrolyte abnormalities that complicate certain malignancies are discussed in detail in other chapters, and hence, are only briefly described in this chapter.

Epidemiology

How common is AKI among cancer patients? The answer depends on the subpopulation of cancer patients of interest, as well as the clinical setting, for example, intensive care unit versus general inpatient service. Also, because the incidence of AKI is dependent on how AKI is defined, comparisons are most reliable if they belong to studies that defined AKI uniformly based on RIFLE (risk, injury, failure, loss, end-stage renal disease), AKIN (acute kidney injury network), or KDIGO criteria

[6–8]. RIFLE criteria define 3 levels of AKI based on the percent increase in serum creatinine from baseline: risk (≥ 50 %), injury (≥ 100 %), and failure (≥ 200 % or requiring dialysis) [9]. Until 3 years ago, when studies of AKI in cancer started adopting RIFLE criteria to define AKI, over 35 different definitions of AKI were used in studies [3], precluding a reliable comparison of findings among studies.

In a Danish population-based study cited earlier [2], the 1-year and 5-year incidence of AKI in the overall cancer population was 17.5 and 27 %, respectively. Cancers of the kidney, gall bladder/biliary tract, liver, bone marrow (multiple myeloma), pancreas, and leukemia confer the highest risk with 1-year risk of AKI of 44, 34, 33, 32, 30, and 28 %, respectively.

In 3558 hospitalized cancer patients, 12 % of patients developed AKI. Notably, 45 % of incident AKI occurred during the first 2 days of admission [3]. By comparison, the published incidence of AKI among patients without cancer is lower (5–8 %) [10, 11]. When the same investigators examined a select cohort of 2398 critically ill cancer patients in the medical and surgical ICU with baseline serum creatinine < 1.5 mg/dL, they reported an overall incidence of AKI to be 12.6 % [4]. This incidence is lower than the historically reported incidence of 13–42 % [12–14]. When the analysis was limited to cancer patients admitted to the medical ICU only, the incidence of AKI was 21 %. The relatively lower overall incidence of AKI in this study was multifactorial: cancer patients with significant baseline CKD were excluded, and the study included a large proportion (58 %) of patients admitted to the surgical service (many electively), who might be expected to have a lower risk of AKI as they are not as acutely ill as patients admitted to medical ICUs.

In the study mentioned above, the cancers associated with the highest incidence of AKI in the ICU setting were hematologic malignancies such as leukemia, lymphoma, and myeloma, with combined AKI incidence of 28 % [4]. This incidence was notably lower than that reported by another recent prospective study that measured the incidence of AKI (defined by RIFLE criteria) among ICU patients with newly diagnosed high-grade hematological malignancies (non-Hodgkin lymphoma, acute myeloid leukemia, acute lymphoblastic leukemia, and Hodgkin disease) who did not show preexisting CKD. The incidence of AKI in this study was 68.9 % [5].

Not surprisingly, among patients with hematologic malignancies, those treated with hematopoietic stem cell transplantation (HSCT) have the highest risk of AKI, with the risk varying with the type of HSCT. Myoablative allogenic HSCT is associated with a higher risk of AKI (> 50 %) [15–19] than nonmyoablative allogenic HSCT (29–40.4 %) [18–20], presumably because the former involves use of a more toxic conditioning regimen. Also, because autologous HSCT is not complicated by graft versus host disease (GVHD), and does not require use of calcineurin inhibitors, it is associated with a relatively lower incidence of AKI (22 %) compared to allogenic HSCT [21].

Four main points may be deduced from these studies: (1) the incidence of AKI among hospitalized cancer patients is higher than that of patients without cancer; (2) acutely ill cancer patients admitted to the ICU have yet higher risk of AKI; (3) some cancers are associated with higher risk of AKI than others; and (4) treatment

with HSCT, especially myeloablative allogenic HSCT, further raises the risk of AKI associated with malignancies.

Causes of AKI in the Patient with Cancer

The etiologic framework of AKI in the patient with cancer is similar to that of noncancer patient in which causes of AKI can be categorized based on the location of the culpable "lesion" as prerenal, intrinsic renal, and postrenal causes (Fig. 1.1). As with AKI in noncancer patients, this approach lends itself to easy application. Although this is a useful construct, certain etiologies of AKI may not neatly fall exclusively into one of the three categories. For instance, some etiologies, such as nephrotoxicity associated with calcineurin inhibitors can be due to both prerenal and intrinsic renal effects due to their effects on vasoconstriction of prerenal and intrarenal vasculature as well as their direct epithelial cell toxicity. Yet, other causes of AKI, such as intravascular hypovolemia may initially lead to prerenal AKI. If the renal ischemia persists, however, it may ultimately lead to tubular injury and necrosis, which moves the etiology into the "intrinsic renal" category. Furthermore the etiology of AKI in cancer patients is often multifactorial.

Prerenal Causes

Sepsis and hypoperfusion are commonly reported causal etiologies of AKI in patients with cancer [22, 23]. Sepsis is an example, however, of a combination of prerenal and intrinsic renal AKI, since sepsis has multiple effects on the tubular epithelial cell as well as the endothelial cell. Sepsis is a common cause of hypovolemia via capillary leak, especially among ICU cancer patients. Cancer patients are prone to developing cancer- or chemotherapy-related conditions that ultimately result in renal hypoperfusion. In a recent study of patients with hematologic malignancies, AKI was caused by renal hypoperfusion in 48.2 % of cases [5]. True intravascular volume depletion often results from diarrhea, vomiting, decreased oral intake, and overdiuresis. Additionally, effective circulating volume declines in the setting of malignant ascites and pleural effusions. Nonsteroidal antiinflammatory drugs (NSAID) and angiotensin converting enzyme inhibitors (ACEI) impair the renal vascular autoregulatory systems, thereby acting synergistically with hypovolemia to create a renal hypoperfused state.

Hypercalcemia, which occurs in 20–30 % of cancer patients over the course of their illness [24], causes vasoconstriction and the associated augmented natriuresis leads to volume depletion. Renal vein thrombosis and impaired cardiac function, for example, due to pericardial effusion, also can contribute to renal hypoperfusion.

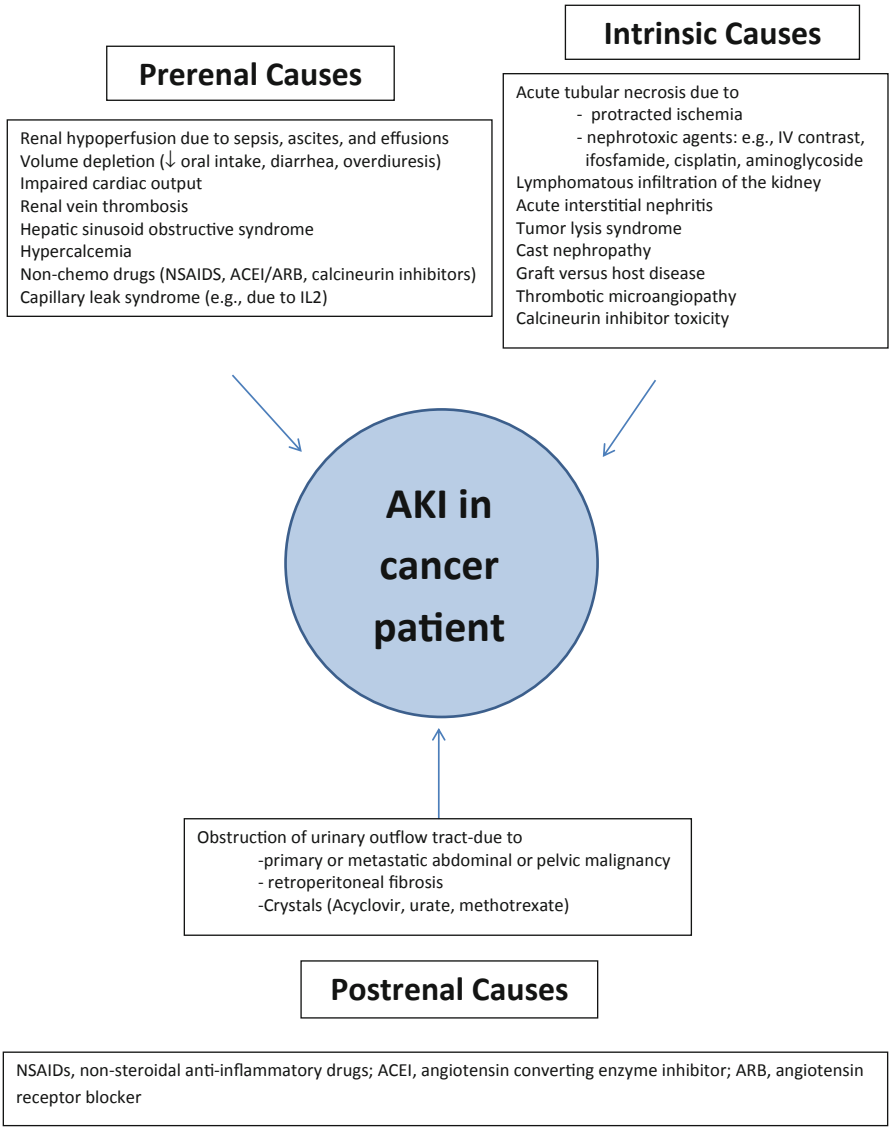

Fig. 1.1 Causes and syndromes leading to acute kidney injury in cancer patients

Likewise, hepatic sinusoidal obstructive syndrome (HSOS), also known as hepatic veno-occlusive disease (VOD), results in "hepatorenal-like" physiology, with impaired renal perfusion.

Case #1
A 56-year-old male with renal cell carcinoma receives an mTOR inhibitor for metastatic disease. Over 2 weeks, a rapid rise in serum creatinine is noted. Urinalysis reveals no red blood cells, white blood cells, or blood. Complete blood count shows a slight decrease in platelet count and no eosinophilia. Granular casts are noted on examination of his urinary sediment. What is the most likely finding in the kidney biopsy?
a. Thrombotic microangiopathy
b. ATN
c. Acute interstitial nephritis
d. FSGS

Intrinsic Renal Causes

Acute tubular necrosis (ATN) is a common, nonspecific endpoint of renal tubular injury. Persistent ischemia from any etiology, and nephrotoxins, including cytotoxic chemotherapy and nephrotoxins released during tumor lysis, result in acute tubular injury. The list of nephrotoxic agents that cause toxic ATN is long. The most common chemotherapeutic agents that have been associated with ATN are presented in Table 1.1. In addition, an entire chapter in this book is dedicated to chemotherapy agents and kidney disease for further details. This list continues to expand to include some ever emerging new chemotherapeutic agents such as inhibitors of mammalian target of rapamycin (mTOR) [25]. It is also important to recognize that there can be significant ischemia to the kidney even though total renal blood flow is preserved if the distribution of renal blood flow leaves important regions of the kidney, such as subsections of the outer medulla, underperfused [26].

It is important to recognize that ATN is a diagnosis, which depends upon evidence that there is necrosis of epithelial cells. ATN is not a clinical diagnosis. The diagnosis can be made noninvasively, however, by observing clear evidence for tubular cell necrosis in the urine sediment. The clinical entity associated with ATN is AKI. The diagnosis of ATN is based on the presence of "muddy brown" or granular casts on urine microscopy. Biopsy is not routinely performed to diagnose ATN, but characteristic findings on renal biopsy include tubular cell degeneration, loss of brush border, apoptosis, and evidence for a reparative response by the tubule, for example, mitotic figures. Immunohistochemical staining shows notable increase in cell cycle-engaged cells and derangement of tubular Na^+, K^+-ATPase expression. There are no radiographic modalities for specifically diagnosing ATN in the clinical setting. As the current diagnostic methods rely on late markers of ATN, diagnosis, and, in turn, treatment of ATN is often delayed. There are ongoing efforts to optimize the use of biomarkers that could diagnose ATN noninvasively, sensitively, and early in the disease process [27–29]

Table 1.1 Chemotherapeutic agents associated with AKI and other forms of kidney injuries

Chemotherapeutic agent	Mechanism of AKI	Clinical presentation	Prophylaxis	References
Azacytidine	Proximal and distal tubular injury	Mild Fanconi syndrome, and polyuria	None established. Self-limiting	[112]
Bisphosphonate (pamidronate, zoledronate)	Acute tubular injury and FSGS	AKI	Avoid use of Zoledronate in patients with CrCl < 35 ml/min. In those patients, reduced doses of pamidronate and ibandronate can be given	[113, 114]
Bevacizumab (and other VEGF inhibitors)	Glomerular endothelial injury, causing TMA; disruption of epithelial slit diaphragms	Proteinuria, HTN, TMA, and AKI	None established	[115, 116]
Cetuximab and panitumumab (monoclonal antibody against EGF receptor)	Deactivation of magnesium channel, TRPM6	Magnesium wasting	None established	[117, 118]
Cisplatin	Toxic damage to renal tubule	AKI, magnesium wasting	Volume expansion, amifostine	[72, 119]–[122]
Cyclophosphamide	Increased ADH activity	Hyponatremia	None established Self-limiting after discontinuation of drug	[76]
Gemcitabine (cell cycle-specific pyramidine antagonist)	TMA	HTN, TMA, proteinuria, and AKI +/− Edema	None established	[123]
Ifosfamide	Proximal +/− distal tubular injury	ATN (often subclinical); Type 2 RTA with Fanconi syndrome; severe electrolyte disarray; nephrogenic diabetes insipidus	Moderate-severe nephrotoxicity generally occur with cumulative doses 100 g/m^2 Avoid concurrent use of cisplatin	[78, 124]
Interferon (alpha, beta, or gamma)	Podocyte injury resulting in MCD or FSGS	Nephrotic syndrome, AKI		[125, 126]

Table 1.1 (continued)

Chemotherapeutic agent	Mechanism of AKI	Clinical presentation	Prophylaxis	References
Interleukin-2	Renal hypoperfusion due to capillary leak, renal vasoconstriction	Hypotension, proteinuria, pyuria	None established	[127, 128]
Methotrexate	Nonoliguric AKI	Tubular obstruction by precipitation of methotrexate and 7-hydroxy-methotrexate	Volume expansion; urinary alkalization; leucovorin rescue; dose reduction for GFR < 10–50 ml/min	[94, 129]
Mitomycin C	AKI	TTP and HUS (associated with cumulative dose > 60mg	None established	[83, 130]
mTOR inhibitors	AKI	ATN, proteinuria	None established	[25]
Nitrosoureas	Glomerular sclerosis and tubulointerstitial nephritis	Insidious, often irreversible renal injury	Volume expansion	[131, 132]

AKI acute kidney injury, *FSGS* focal segmental glomerulosclerosis, *CrCl* creatinine clearance, *TMA* thrombotic microangiopathy, *HTN* hypertension *ATN* acute tubular necrosis

Case #1 Follow-Up and Discussion
The patient presented previously, shows ATN in the presence of a urine sediment with granular muddy brown casts. As noted above mTOR inhibitors have been reported to cause ATN as well as proteinuric renal diseases.

It is not always the case that the correction of renal ischemia, resolution of septic shock or removal of an offending nephrotoxin, leads to complete resolution of ATN. The initial insult may result in a repair process that is incomplete and maladaptive. This may not be initially apparent, but is supported by the higher risk of future CKD [30–32]. Therefore, prevention of ATN should be the goal. Prophylaxis against ATN is aimed at hemodynamic optimization, intravascular volume expansion with crystalloids or diuresis, to augment cardiac filling and renal perfusion and reduce intrarenal concentrations of nephrotoxic agents. The approach also involves avoiding sepsis and treating the cancer before it has an impact on renal function either directly or indirectly. Once AKI is established, treatment is aimed at optimizing hemodynamic support, treating sepsis if it is present and withdrawing or reducing the dose of the nephrotoxic agent if possible.

Lymphomatous Kidney Infiltration (LIK)

Lymphomatous kidney infiltration is common, albeit underdiagnosed, among cancer patients. Its incidence ranges from 6 to 60 % in autopsy series [33]. In the largest autopsy case series comprising 696 cases of malignant lymphoma, LIK was found in 34 % of cases, although only 14 % were diagnosed before death. Although kidney infiltration was bilateral in the majority (74 %) of cases, it was associated with acute renal failure only in 0.5 % of cases [34]. It must be considered however that the definition used for acute renal failure in 1962, when this paper was published, is very different from the one used today for AKI. This supports the observation that LIK is a common complication of hematologic malignancies, but may not be a common cause of severe AKI in these patients.

The reason for LIK underdiagnosis is multifactorial. Most patients with LIK have no clinical renal manifestations [33], and when present, clinical manifestations such as flank pain, hematuria, abdominal pain, palpable mass, hypertension, and subnephrotic range proteinuria—are not specific to LIK [33, 34]. While lymphoma cells may be present on urinalysis they frequently go unnoticed. Common findings on urinalysis are mild proteinuria, few red blood cells, white blood cells, and granular casts. The sensitivity of radiographic diagnosis is also poor with diagnosis of LIK by computed tomography imaging in the range 2.7–6 % [35]. While LIK is almost always diagnosed by renal biopsy [36], a biopsy is not frequently obtained because cancer patients with LIK often have nonrenal cancer complications to which their renal insufficiency may be ascribed. Concurrent coagulopathy in the acutely ill cancer patient is often seen as a relative contraindication to renal biopsy. A kidney biopsy is pursued when the diagnosis of LIK would prompt initiation or modification of chemotherapeutic agents.

The mechanism of LIK-induced AKI is not completely established. Since tubules and glomeruli usually appear morphologically normal on biopsy, it has been proposed that interstitial and intraglomerular pressure elevation due to lymphocytic infiltrations of these compartments is the underlying mechanism of the AKI [33, 36]. Proponents of this mechanism also point to improved renal function with chemotherapy being supportive of this hypothesis. Complete renal recovery to baseline function is not frequent [37]. Management of LIK is focused on treatment of the underlying malignancy.

Myeloma Cast Nephropathy

Renal impairment affects 20–40 % of newly diagnosed patients with multiple myeloma (MM) [38, 39]. Some case series report that up to 10 % of patients with newly diagnosed multiple myeloma have AKI severe enough to warrant dialysis [39, 40]. While cast nephropathy is not the sole etiology of AKI in patients with multiple myeloma, cast nephropathy is the most common finding on renal biopsy, found in 41 % patients biopsied with monoclonal gammopathies [41]. In this cohort,

AL-amyloidosis was found in 30 %, light chain deposit disease in 19 %, tubulointerstitial nephritis in 10 %, and cryoglobulinemic kidney lesions with MM in 1 patient. Factors that promote cast formation and AKI in myeloma include dehydration, delivery of high burden of serum-free light chains to the distal nephron, acidic urine, concurrent use of furosemide or NSAIDs, hypercalcemia, and intravenous contrast use [42, 43].

The majority of studies show that AKI in patients with MM is associated with increased morbidity and mortality [44–46]. By contrast, in one case series, when adjusted for the stage of MM, renal failure had no impact on survival [47]. It was suggested that, as renal function is closely correlated with myeloma cell mass [48], the correlation between renal impairment and increased mortality may be more reflective of the burden of MM than that of renal impairment per se [49]. It is noteworthy that in other malignancies, as in noncancer patients, AKI correlates with increased morbidity and mortality. It will be surprising if this is not the case in MM as well. Treatment of renal disease associated with myeloma is discussed elsewhere in this book.

Case #2
A 56-year-old male is noted to have subacute rise in serum creatinine and development of hematuria and proteinuria. Serological workup is negative but serum-free light chains revealed an abnormal ratio of elevated kappa to lambda of 9 (serum creatinine is 1.5 mg/dl). A bone marrow study revealed MGUS (monoclonal gammopathy of undetermined significance) with only 4 % IgG kappa plasma cells. A kidney biopsy revealed a MPGN pattern of injury with immunofluorescence positive for IgG kappa. How do you proceed with treatment?

a. Start steroids for treatment of MPGN
b. Treat underyling B cell clone in the bone marrow and treat this as monoclonal gammmopathy of renal significance
c. Repeat the bone marrow
d. No treatment till plasma cells are > 10 % and a diagnosis of myeloma is made.

Membranoproliferative Glomerulonephritis Secondary to Monoclonal Gammopathies

The spectrum of renal injury associated with monoclonal gammopathy is broad [50]. While, as stated above, the majority of kidney diseases associated with monoclonal gammopathies are due to the deposition of light chains [51], it is becoming increasingly recognized that an immune complex glomerulonephritis can occur. This is characterized by subendothelial and mesangial immune complex deposition and is

an underappreciated cause of kidney injury caused by monoclonal gammopathies both in native kidneys [52] as well as in renal allografts [53].

Case #2 Follow Up and Discussion
In a large biopsy case series, the incidence of monoclonal gammopathy-associated MPGN was higher than hepatitis-associated MPGN and was nearly equivalent to the incidence of myeloma kidney [52]. This study highlights the important point that MPGN is associated with a wide spectrum of plasma cell and lymphoproliferative disorders, ranging from multiple myeloma at one extreme and MGUS at the other end of the spectrum. Because many patients with MPGN have underlying monoclonal gammopathy, there is a need for careful investigation before using the diagnostic label of MGUS—because what may appear as "undetermined significance" may be causally associated with MPGN. Similarly, before diagnosing idiopathic MPGN, a full work-up for gammopathies—including serum electrophoresis—should be undertaken. Patients with monoclonal gammopathy have an incidence of MPGN recurrence that is twice of that seen in patients without monoclonal gammopathy (66.7 vs. 30 %) [54]. Because kidney biopsies are generally delayed—especially, when anti-GBM or pauci immune diseases are not the suspected etiology of AKI, it is unknown how frequently AKI is the initial presentation of MPGN. It is likely, however, that more MPGN cases present initially as AKI than appreciated. Awareness of this possibility will increase the likelihood of early diagnosis and treatment. Based on the above discussion, the patient in case 2 should be treated promptly for the underlying B cell clone that is present in the bone marrow and affects the kidney. This is MGRS (monoclonal gammopathy of renal significance) and not MGUS anymore. Watchful waiting might lead to ESKD. Since there appears to be a secondary cause of MPGN in this case, steroids alone will not be sufficient. The correct answer is b.

Tumor Lysis Syndrome (TLS)

TLS is the most common oncologic emergency [55] with incidence as high as 26 % in high-grade B-cell acute lymphoblastic leukemia [56]. TLS results from rapid release of intracellular contents of dying cancer cells into the bloodstream either spontaneously or in response to cancer therapy. It is biochemically characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Cardiac arrhythmias, seizures, and superimposed AKI are common clinical presentations. The pathophysiology of TLS-mediated AKI involves intratubular obstruction and inflammation by precipitation of crystals of uric acid, calcium phosphate and/or xanthine. Preexisting renal dysfunction favors intratubular crystal precipitation [57]. Consensus recommendations for TLS prophylaxis include volume expansion for

all risk groups, use of allopurinol in medium- and high-risk groups, and use of recombinant urate oxidase (rasburicase) in high-risk groups [58]. Care should be taken, however, with use of this agent, which converts uric acid to allantoin, carbon dioxide, and hydrogen peroxide, since the latter can lead to methemoglobinemia and hemolytic anemia in individuals with glucose-6-phosphate deficiency. Utility of diuretics and urine alkalization are variable and their efficacy is debatable [58]. A chapter of this book has been devoted to TLS.

AKI Following Hematopoietic Stem Cell Transplantation (HSCT)

AKI is a common and consequential complication of HSCT. Causes of AKI following HSCT are divided into early onset (< 30 days) or late onset (> 3 months) [42]. Early AKI is commonly caused by sepsis, hypotension, and exposure to nephrotoxic agents [42]. Moreover, TLS and hepatic sinusoidal obstruction syndrome (HSOS) are also causes of early AKI with onset within 30 days of HSCT. Late onset AKI is often due to either thrombotic microangiopathy (TMA) or calcineurin inhibitors (CNIs) toxicity [15, 42].

The incidence of AKI varies according to the type of HSCT: AKI is less frequent after autologous HSCT when compared to allogenic HSCT because the former patient is spared the nephrotoxicity of CNI, which is used for treating GVHD prophylaxis in the latter. Similarly, a nonmyeloablative conditioning regimen is associated with lower risk of AKI than a myeloablative conditioning regimen because the former involves use of a less intense regimen and lower risk of HSOS.

The diagnosis of TMA is often delayed because many of its characteristic features— anemia, thrombocytopenia, AKI, elevated serum LDH—are nonspecific and are common findings in cancer patients post-HSCT in the absence of TMA. The presence of schistocytes and hypertension can be helpful but alone are not sufficient for a definitive diagnosis. A high index of suspicion is required for a diagnostic workup for TMA to be initiated. If a biopsy is done, it often shows mesangiolysis, GBM duplication, glomerular endothelial swelling, tubular injury and interstitial fibrosis [42, 59]. Except for atypical cases or situations where the management course would be altered, a kidney biopsy is often not required. Management of HSCT-associated TMA is supportive, and often involves discontinuation of CNIs—because CNIs are known to increase the risk of HSCT-associated TMA [42, 60].

Hepatic sinusoidal obstruction syndrome (HSOS) is characterized by sinusoidal and portal hypertension that result from radio-chemotherapy-induced endothelial cell injury of hepatic venules [60]. AKI develops in nearly 50 % of HSCT patients who develop HSOS [15, 42]. The pathophysiology of HSOS-associated AKI is similar to hepatorenal physiology, characterized by fluid-retention, sodium retention, low urinary sodium, peripheral edema, weight gain, and usually bland urine sediment. Notably, more than 70 % of patients with HSOS will recover spontaneously with only supportive care—managing sodium and water balance, augmenting renal perfusion, and relieving symptomatic ascites with repeated paracentesis [42, 61]. For details on HSCT-associated renal disease, refer to a related chapter in this book.