Surgery in Metastatic RCC

Removal of the primary renal tumor in the face of metastatic disease (i.e., debulking or cytoreductive nephrectomy) is pursued in patients with good performance status, limited extrarenal disease, and low comorbidities. Two randomized trials have shown an overall survival benefit in these circumstances. In addition, surgical removal of solitary metastatic sites is associated with disease control in up to 30% of highly selected patients.

Systemic Therapy for Metastatic RCC

The initial treatments for metastatic RCC—hormone therapy and chemotherapy—produced only minimal benefits (Table 58-1). Immunotherapy has yielded modest benefits, majority of benefit realized in highly selected patients who have a durable complete response to high-dose interleukin-2. The major treatment advance in metastatic RCC was the discovery of the reliance of the cancer on the vascular endothelial growth factor (VEGF) pathway, which results from *VHL* gene inactivation. This led to the clinical development of a number of VEGF pathway inhibitors, as outlined in Table 58-1. In general, 70% to 75% of patients who receive these drugs have some reduction or stabilization of tumor burden. Periods of disease control typically last for some months, although they can extend to several years in a small minority of patients. Combinations of existing agents are more toxic and no better than monotherapy. The current standard of care is a sequence of monotherapies with agents targeted to VEGF and/or mammalian target of rapamycin (mTOR).

Prognosis

The prognosis of localized kidney cancer is determined largely by the stage and grade of the primary tumor. Other systems have been based on other features, such as tumor necrosis, symptoms at presentation, or performance status. In metastatic disease, established schema associated with prognosis use performance status, time from diagnosis to metastatic disease, and laboratory values (lactate dehydrogenase [LDH], hemoglobin, calcium, neutrophils, and platelets).

BLADDER CANCER

Definition and Epidemiology

Urothelial carcinoma of the bladder (UCB) represents 4% of all malignancies and about 3% of cancer-related deaths in the United States. It is more common in developed countries and is the fourth most common cancer among men and ninth among women in the Western world. Smoking is an established risk factor for bladder cancer; the incidence rate is four times higher for smokers than for nonsmokers. Occupational exposures from a range of agents that contain aromatic amines, as chlorinated hydrocarbons and polycyclic aromatic hydrocarbons, are believed to account for up to 20% of all bladder cancers. Genetic susceptibility is increasingly recognized as an important risk factor. The risk of bladder cancer is doubled in first-degree relatives of patients with bladder cancer. Inherited genetic factors, such as the slow acetylator *N*-acetyltransferase 2 (NAT2) variants and the glutathione *S*-transferase Mu 1 (GSTM1)–null genotypes, are established risk factors.

Pathology

Transitional cell carcinoma is the predominant histologic subtype in the United States and Europe, where it accounts for 90% of all bladder cancers. Adenocarcinoma, squamous cell carcinoma, and small cell cancers account for most of the remaining 10%, although there are parts of the world where nonurothelial carcinomas are more common. The bladder wall consists of four layers: urothelium (the innermost epithelial lining), lamina propria, muscularis propria (detrusor muscle), and adventitia (serosa).

Clinical Presentation

UCB is more common in males (4:1), and the median age at presentation is 73 years. Approximately 75% of newly diagnosed cases of UCB are not muscle invasive; the remaining 25% exhi bit de novo invasion of the muscle wall of the bladder at presentation.

Patients with bladder cancer typically have painless hematuria at presentation, although irritative voiding symptoms (frequency, urgency, and dysuria) can be the initial manifestation. Patients with more advanced disease may have progressive flank or pelvic pain from direct extension of disease or as a consequence of ureteral obstruction.

Diagnosis and Differential Diagnosis

The initial evaluation typically involves an office-based cystoscopic evaluation, with the collection of urine for cytology. Subsequently, patients undergo a transurethral resection of bladder tumor (TURBT) under anesthesia to obtain tissue for histologic

TABLE 58-1 SUMMARY OF THERAPEUTIC APPROACHES IN METASTATIC RCC

AGENT	OBJECTIVE RESPONSE RATE	PFS (mo)	COMMENTS
Hormonal therapy	2%	N/A	Limited, palliative role in the treatment of metastatic RCC
Chemotherapy	5-6%	N/A	Not generally used
Interleukin-2	~20-25% (high dose)	3.1	Durable complete response rate of 7-8%
Interferon alfa	10-15%	4.7	Modest improvement in overall survival compared with inactive therapy
VEGF inhibitors*	Approximately 30%	9-11	Common toxicity includes fatigue, mucositis, hand-foot syndrome, diarrhea, hypertension, and hypothyroidism
mTOR inhibitors†	2% (treatment refractory) to 9% (treatment naive)	4-7	Increased overall survival of temsirolimus monotherapy vs IFN monotherapy in poor-risk patients Toxicity includes fatigue, mucositis, rash and hypertriglyceridemia/hyperglycemia/hypercholesterolemia

IFN, Interferon; mTOR, mammalian target of rapamycin; N/A, not applicable; PFS, progression-free survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
*VEGF inhibitors: sorafenib, sunitinib, pazopanib, axitinib.
†mTOR inhibitors: temsirolimus, everolimus.