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Nonsurgical Management of Metastatic Renal Cell Carcinoma

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The management of advanced renal cell carcinoma (RCC) has evolved greatly in recent years. The role and benefit of debulking nephrectomy has been more clearly defined. Long-considered an immunoresponsive tumor, cytokines such as interferon-\(\alpha\) (IFN-\(\alpha\)) and interleukin-2 (IL-2) evolved into the standard initial treatment for advanced RCC through clinical trials in the 1980s and 1990s. More recently, a growing understanding of the biology underlying some RCC tumors has led to the clinical testing of therapeutics that target vascular endothelial growth factor (VEGF). These recent trials have produced robust clinical results that have evolved the standard of care and introduced new treatment options in this historically treatment-refractory disease. This chapter focuses on standard cytokine therapy for advanced RCC as well as VEGF-targeted approaches. In addition, certain aspects of supportive care, including treatment of central nervous system (CNS) metastases and use of bisphosphonates for bone metastases, are discussed.

Debulking Nephrectomy

Debulking nephrectomy has become a standard of care in selected metastatic RCC patients on the basis of two identically designed, prospective randomized trials (1). Eligibility for both trials, based on the tumor, node, metastasis (TNM) grade, included biopsy-proven \(T_{\text{any}}\), \(N_{\text{any}}\), M1 RCCs with a primary tumor amenable to resection as determined by the operating surgeon. Additional eligibility included Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, no prior radiotherapy or systemic treatment of any kind, and adequate end-organ function. Eligible patients were randomized to radical nephrectomy (with or without lymphadenectomy), followed within 1 month after surgery by interferon-\(\alpha\) (5 million units subcutaneously \(3 \times /\text{week}\)) or to immediate interferon without preceding nephrectomy. Both trials were powered to detect an overall survival improvement, with analysis based on intent-to-treat criteria using Kaplan-Meier technique for survival duration. A combined analysis of 341 total randomized patients demonstrated an overall survival advantage for the
nephrectomized group of 13.6 months versus 7.8 months \((p = .002)\). Not surprisingly, the benefit was most pronounced in performance status 0 patients, but was not dependent on the site of metastasis or disease measurability. The combined response rate in 253 patients with measurable disease revealed a 6.9% response rate in the nephrectomy arm vs. a 5.7% response rate in the interferon only arm \((p = .60)\). Surgical morbidity and mortality were acceptable and did not prevent subsequent administration of interferon in 95% of nephrectomized patients a median of 19 days after surgery.

These trials provide convincing evidence of an overall survival benefit in appropriately selected patients. These data have been translated into the clinical practice of initial debulking nephrectomy followed by systemic therapy. Importantly, proper patient selection can maximize the benefit of this approach. Patients with good performance status, a resectable primary tumor representing the majority of tumor burden, and without rapidly progressing extrarenal disease or medical comorbidities should be considered for initial nephrectomy.

**Cytokine Therapy in Advanced Renal Cell Carcinoma**

Although a mainstay of cancer therapeutics for decades, the exact mechanism of IL-2 in RCC is largely unknown. Interleukin-2 is a cytokine that stimulates activated T cells and natural killer (NK) cells, inducing an antitumor immune response \((2)\). Interferon-\(\alpha\) is a naturally occurring glycoprotein produced in response to viral infections and foreign antigens. It has been investigated as an antitumor agent in a variety of diseases including RCC with postulated mechanisms of action including immunomodulation \((3,4)\), antiproliferative activity \((5)\), and inhibition of angiogenesis \((6)\). In metastatic RCC, varying doses, schedules, and combinations of these cytokines have been investigated.

**High-Dose Interleukin-2**

Two large randomized trials have examined the benefit of high-dose (HD) IL-2 in comparison to low-dose cytokine regimens. The Cytokine Working Group randomized 193 cytokine-naive metastatic RCC patients to HD IL-2 \((600,000\ \text{units/kg IV q8h} \times 14\ \text{doses; maximum three cycles})\) or low-dose subcutaneous (sc) IL-2 \([5\ \text{million units (MU)/m}^2\ \text{5 days/week} + \text{IFN 5 MU/m}^2\ \text{3 days/week}]\) \((7)\). The primary end point was progression-free survival at 3 years. The overall response rate was 23% for HD IL-2 vs. 10% for low-dose cytokines \((p = .018)\), and the median response duration for HD IL-2 was 24 months, compared with 15 months for IL-2 and IFN \((p = .18)\). However, no significant difference in 3-year progression-free survival \((10\%\ vs.\ 3\%; p = .082)\) or overall survival \((17\ \text{months vs. 13 months; } p = .21)\) was observed. There were a substantially increased number of grade 3/4 toxicities in HD IL-2 arm.