Renal Cell Carcinoma

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Summary

Renal cell carcinoma (RCC) accounts for 2–3% of all malignancies; however, its incidence has increased by 43% since 1973, with a 16% increase in the death rate. It is estimated that, in 2005, more than 36,000 new cases of kidney cancer will be diagnosed in the USA, and there will be 12,660 deaths. The recent Food and Drug Administration’s (FDA) approval of two multi-tyrosine kinase inhibitors and encouraging results from a phase III trial of a mammalian target of rapamycin (mTOR) inhibitor represent significant advances in the treatment of metastatic renal cancer. An increased understanding of molecular oncology and cancer genetics has identified multiple genetic and cell-signaling defects in RCC that are prime targets for novel therapies.

Key Words: Renal cell carcinoma; molecular therapy.

1. INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2–3% of all malignancies; however, its incidence has increased by 43% since 1973, with a 16% increase in the death rate (1,2). It is estimated that, in 2005, more than 36,000 new cases of kidney cancer will be diagnosed in the USA, and there will be 12,660 deaths (3). Approximately, 20–30% of patients will have metastatic disease at initial diagnosis, and 20–40% of patients with localized RCC who undergo nephrectomy will develop metastases (4). The survival of patients with metastatic renal cancer is poor, with a median survival of less than 1 year (5).

RCC is a collection of different neoplasms with distinct histologies and varying responses to therapy. The most common renal cell cancer is clear cell, accounting for approximately 75% of localized renal tumors and thought to originate from the proximal tubal epithelium (6). Other histologic types include papillary (15%), chromophobe (5%), medullary (<2%), X-translocation tumors (<1%), and benign oncocytsa (5%).

Molecular expression analyses suggest that additional subtypes may exist (7).
Surgery remains the mainstay of therapy for localized RCC (8). Treatment of metastatic RCC remains a challenge, as renal tumors are not radiosensitive and few cytotoxic chemotherapies have shown consistent responses. Before the development of tyrosine kinase inhibitors sorafenib and sunitinib, cytokine-based immunotherapy with interferon (IFN)-α and interleukin (IL)-2 was the cornerstone of therapy for metastatic RCC. In 1992, the FDA approved high-dose IL-2 for treatment of metastatic RCC. The overall response rate for high-dose IL-2 in metastatic RCC is 15–20%, including some complete responders (9). However, this therapy has considerable toxicities, including hypotension, respiratory distress, and renal impairment; also, high-dose IL-2 requires administration in hospital ward with specialized nursing care. A phase III trial compared high-dose IL-2 (720,000 U/kg) with low-dose IL-2 (72,000 U/kg) (10). Whereas low-dose IL-2 had considerably fewer toxicities, high-dose therapy had significant higher responses (21% versus 13%, \(p = 0.048\)). IFN-α monotherapy has been studied in several trials and appears to be superior to placebo with a survival advantage of 3.8 months and response rate of approximately 15% in randomized phase III trials (11).

Although there are considerable side effects to IFN-α, such as fever, malaise, and flu-like symptoms, it is less toxic than high-dose IL-2 and can be administered at home by the patient. Various combination IL-2 and IFN-α regimens have been described, and recently, a phase III study of high-dose IL-2 versus IFN-α/IL-2 was reported (12). This trial reports a higher response rate with high-dose IL-2 in comparison with IFN-α/IL-2 (23% versus 9.9%, \(p = 0.018\)); however, the median duration of response and the median survival were not statistically significant. Chemoimmunotherapies have not been shown to be any more effective than IL-2 and/or IFN-α.

It appears that low-dose immunotherapy has a modest antitumor and survival benefit, whereas high-dose IL-2 leads to durable complete responses in a small proportion of patients. It would therefore be useful to identify patients most likely to benefit from the latter very toxic regimen. To this end, data strongly suggest that non-clear cell renal carcinomas do not benefit from IL-2 or IFN-α. More recent data identify a subgroup of well-differentiated clear cell cancer patients who are most likely to benefit from high-dose IL-2, and there is accumulating evidence that high tumor expression of carbonic anhydrase IX (CAIX) may help identify this subgroup (13). Further research in this area is clearly necessary. Additionally, with the emerging positive clinical data with novel therapies for renal cancer, the role of immunotherapy will be diminished.

Therapy for metastatic renal carcinoma has thus remained a challenge for physicians. An increased understanding of molecular oncology and cancer genetics has identified multiple genetic and cell-signaling defects in RCC that are prime targets for novel therapies. The use of novel therapies in renal cancer has gained momentum recently with the FDA approval of two multi-tyrosine kinase inhibitors and encouraging results from phase III trial of a mammalian target of rapamycin (mTOR) inhibitor. In the subsequent sections, we will outline molecular abnormalities in renal cell cancer and review novel therapies that are in development and that will likely change the approach to this disease. Table 1 summarizes potential therapeutic targets and drugs discussed in this chapter. Previously described cytotoxic and other immunotherapies have been the subject of other reviews and will not be discussed further here (14,15).