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Failure of Cytotoxic Chemotherapy, 1983–1988, and the Emerging Role of Monoclonal Antibodies for Renal Cancer

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Abstract. A review of 36 cytotoxic agents used singly in over 1,900 patients with renal cancer between 1983 and 1988 finds marginal antitumor activity, <5–10%. The future role of monoclonal antibodies for therapy of this disease may offer some hope with the recent description of rather specific phenotypic expression, URO 10^+/URO 8^+, suggesting the cell origin of most renal tumors from the distal portion of the proximal tubule.

Introduction

The most effective therapy for renal cell carcinoma remains surgery; albeit, efficacy has only been demonstrated for locoregional resectable disease. Irradiation plays a limited role, primarily for treatment of central nervous system, spinal cord, osseous, and selected soft tissue metastases. Cytotoxic chemotherapy, an integral part of the therapeutic approach for many solid tumors, has demonstrated little or no antitumor activity against advanced renal cell cancer and, therefore, has played no role adjuvantly or neoadjuvantly.

Previous reviews of trials for renal cell carcinoma in 1977 [1] and in 1983 [2] found most cytotoxic and hormonal agents induced remission in only 0–10% of cases, a rate that may simply represent 'background noise'. With the absence of significant antitumor response with single agents, it is not surprising that multidrug combination regimens also proved ineffective when evaluated in prospective trials against a single drug. This paper reviews the 6 years of cytotoxic chemotherapy between 1983 and 1988, and discusses the emerging role of immunological and biological agents.

Response Criteria

While phase I trials are designed to evaluate the pharmacokinetics and toxicology of new experimental or investigational agents in order to determine the maximally tolerated dose and schedule, phase II studies, primarily disease-oriented ones, are undertaken in a limited number of cases with bidimensionally measurable parameters to define efficacy. Previously, the mechanism of phase II studies involved broad drug-oriented trials permitting entry of patients who had had prior cytotoxic drugs, as well as unidimensional or poorly evaluable lesions which frequently precluded a clear end point of response. More recently, phase II trials have mostly been limited to unpretreated cases since there is strong evidence that exposure to 1 agent may activate the multidrug resistant gene mdr-1 which can prevent response to another agent [3]. This silent statistician, patient and tumor selection, has influenced results of trials in other solid tumors. Unfortunately, data indicate renal cell carcinoma, as well as adrenal cell and colon cancer, already possess mdr-1 gene activation, thereby explaining the relative failure of cytotoxic agents in such tumors.