The High-Dose Aldesleukin (IL-2) “Select” Trial: A Trial Designed to Prospectively Validate Predictive Models of Response to High-Dose IL-2 Treatment in Patients With Metastatic Renal Cell Carcinoma

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Abstract

For patients with metastatic renal cell carcinoma (RCC), the prognosis is poor. Despite the recent approval of drugs such as sorafenib, sunitinib, and temsirolimus, durable remissions of metastatic disease are rare. This is largely due to the fact that these drugs, while effective, do not result in the eradication of disease. In 1992, the FDA approved the use of high-dose interleukin-2 (IL-2) for the treatment of patients with metastatic RCC because of the small number of patients that achieved durable responses. However, IL-2 has not become a mainstay of treatment because of the expense and toxicity associated with this therapy. This review article discusses a phase II trial that investigates predictive biomarkers that might help clinicians identify the patient population with metastatic RCC that would benefit from IL-2 therapy and therefore limit patients who receive this toxic therapy to those most likely to benefit.

Introduction

The prognosis for patients with recurrent and or metastatic renal cell carcinoma (RCC) is poor, as median survival is 10-13 months and 5-year survival is < 5%.1-4 Chemotherapy has limited activity, and though interferon-α (IFN-α) can produce marginal survival benefits, response rates are 5%-15% and most of these responses are partial and short-lived.5-8 More recently, the treatments for these patients have included tyrosine kinase inhibitors (TKIs) such as sunitinib and sorafenib, and the mammalian target of rapamycin (mTOR) inhibitor temsirolimus. Though both TKIs and temsirolimus have shown improvement in median progression-free survival, none have demonstrated durable responses.9-14 In contrast, the administration of high-dose bolus interleukin (IL)-2 has produced durable responses in a modest percentage of patients with RCC.15 High-dose bolus IL-2 should be considered for appropriately selected patients,16 but given the toxicity, expense, and limited availability of this treatment, appropriate patient selection criteria need to be re-evaluated and further investigated. Recent studies suggest that the potential exists for identifying predictors of response and limiting therapy to those most likely to benefit. Thus, a phase II trial to prospectively identify predictors of response was designed to determine which patients will be most likely to benefit.

Background and Rationale

In 1992, high-dose bolus IL-2 was approved by the FDA for the treatment of patients with metastatic RCC based on data presented from 7 phase II
clinical trials.15 In these studies, objective responses were seen in 15% of patients. Complete responses (CRs) were seen in 7%, and 8% of patients had partial responses (PRs). The median duration of response was 54 months for all responders, 20 months for PRs, and has not yet been reached for CRs. The median survival was 16 months for all 255 patients.

To further delineate the role of high-dose IL-2, the Cytokine Working Group (CWG) performed a phase III trial that randomized patients to either outpatient IL-2 and IFN-α every 6 weeks or standard high-dose inpatient IL-2 every 12 weeks.17 The response rate for high-dose IL-2 was 23% versus 10% for IL-2/IFN-α. The median response durations were 24 months for high-dose IL-2 and 15 months for IL-2/IFN-α. Median overall survival for high-dose IL-2 was 17.5 months compared with 13 months for IL-2/IFN-α. These studies highlight that high-dose IL-2 is superior to low-dose cytokines in terms of response rate and the possibility of durable responses.

**Correlative Studies**

Many groups have attempted to determine reliable clinical predictors of response and survival for patients with metastatic RCC who were receiving immunotherapy.15,18-29 Some investigators have begun to examine tumor tissue to identify molecular markers that might predict the outcomes of patients with RCC. Carbonic anhydrase IX (CAIX) has been identified as one potential marker. CAIX is thought to play a role in cell proliferation in response to hypoxic conditions and its expression is mediated by the HIF-1α transcriptional complex and induced in many tumors types, but is absent in most normal tissue with the exception of epithelial cells of the gastric mucosa. Bui et al used a monoclonal antibody designed to detect CAIX expression to perform an immunohistochemical analysis of paraffin-embedded RCC specimens.30 In their analysis, high CAIX expression in primary tumors was seen in 79% of patients and was associated with improved survival and possibly response to IL-2–based therapy. All long-term responders to IL-2–based treatment had high CAIX expression and level of CAIX expression was an independent predictor of outcome.

Subsequently, Atkins et al performed a nested case control study within a larger cohort of patients whose pathology was analyzed.31 CAIX expression levels were correlated with response to IL-2, pathologic risk categorization and survival. The percentage of CAIX-positive tumor cells was used to separate high (> 85%) and low (≤ 85%) expressors. Sixty-two percent of samples had high CAIX expression. Seventy-eight percent of the responding patients had high CAIX expression compared with 51% of nonresponders, giving an odds ratio of 3.3 (P = .04). Median survivals were 3 years and 1 year for high and low CAIX expressors, respectively (P = .04). Survival > 5 years was only seen in the high CAIX expressing group. High CAIX staining was associated with better pathology features but remained an independent predictor of response.

**Study Objective**

The primary objective of this study is to determine, in a prospective fashion, if the predictive model proposed based on the Atkins et al study can identify a group of patients with advanced RCC who are significantly more likely to respond to high-dose IL-2–based therapy than a historical, unselected patient population.15,31 Another objective is to prospectively determine the response rate to high-dose IL-2 for patients with metastatic RCC and “poor” pathologic and molecular predictive features. The study will assess if components of other predictive and prognostic models can help to further define the optimal population to receive high-dose IL-2 for metastatic RCC. Baseline immune function, immunohistochemical markers, or gene expression patterns that might be associated with response to high-dose IL-2 therapy will also be explored to further narrow the application of IL-2.

**Study Design**

This is an open-label phase II prospective study. Eligible patients receive treatment with IL-2 alone following the FDA-approved schedule. Patients will be evaluated for response at approximately 7 and 11 weeks following the beginning of their treatment course by computed tomography or magnetic resonance imaging. Following completion of therapy, patients with evidence of an antitumor effect will have imaging every 3 months for 2 years, then every 6 months during year 3 and then yearly thereafter for years 4 and 5. All patients will be followed until death. Time of disease progression and time of initiation of alternate therapies will be documented. Correlative studies on pathologic specimens and blood samples will be performed to evaluate for novel markers that might predict for response.

**Treatment Regimen**

Treatment with IL-2 (dose = 600,000 IU/kg, manufactured by Novartis) will begin on day 1 and continue approximately every 8 hours for a maximum of 14 doses each cycle. The dosing schedule can be adjusted to allow for patients to recover from toxicity. Treatment will begin again on day 15 using the every-8-hour schedule for a maximum of 14 doses, if all toxicity has returned to grade 1 or less. The second cycle of therapy may be delayed up to 1 week to allow toxicity to resolve. The maximum number of doses that can be administered during one course will be 28 doses.

**Dose Modification Scheme**

Modification of the treatment protocol will occur by withholding doses of IL-2 rather than continuing therapy at a reduced dose. Dose of IL-2 will be withheld for (1) refractory hypotension, (2) anuria for > 24 hours, (3) respiratory distress, (4) confusion, (5) sustained ventricular tachycardia, signs of myocardial ischemia, or myocarditis, (6) persistent metabolic acidosis, (7) atrial fibrillation, and (8) documented systemic infection, or any serious toxicity not controlled at time of next dose.

**Salient Eligibility Criteria**

**Inclusion Criteria**

Patients must have a diagnosis of histologically confirmed RCC of any histologic type that is metastatic or unresectable, with measurable disease, access to tissue blocks containing adequate tumor for interpretation and analysis, good performance status, adequate organ function as evidenced by laboratory values and cardiopulmonary testing, recovered from any effects of major surgery and be free of significant detectable infection, and no contraindication to the use of vasopressor agents. Patients may not have had previous
radiotherapy to areas of measurable disease unless they have progressive disease in this site or measurable disease outside the area of previous radiation.

Exclusion Criteria

Patients will be excluded from this trial if they have received systemic therapy for metastatic disease, have organ allografts, require or are likely to require systemic corticosteroid for intercurrent illness. Patients with any significant medical disease, which would significantly increase the risk of immunotherapy, are also excluded. Patients may not have a history of another malignancy within the past 5 years other than surgically cured nonmelanoma skin cancer, carcinoma-in-situ, or stage I carcinoma of the cervix. Patients with brain metastases, leptomeningeal disease, or seizure disorders are ineligible.

Statistical Design

The goal is to enroll 66 patients with good predictive factors. The best overall response rate is expected to be between 30%–40% based on previous trials and the pathology and CAIX model paper of Atkins et al. The sample size is selected such that the 95% CI for a response proportion of 0.30 will have precision (half-width) of < ± 0.14 so that the lower confidence limit for a 0.30 response is above a 0.15 response proportion expected in an unselected population of patients and such that there is 80% power for a 1-sample hypothesis test with 2-sided α = 0.05. A sample size of 66 produces an exact 96% CI equal to the sample proportion ± 0.109 when the estimated response proportion is 0.30, and there is 81% power for a 1-sample hypothesis test.

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Disclosures

Dr. David F. McDermott has served on an Advisory Board and Speaker’s Bureau for Novartis Pharmaceuticals Corporation, and has served as a consultant or been on an Advisory Panel for Genentech, Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; and Wyeth Pharmaceuticals.

Dr. Jessica M. Clement has no potential conflicts of interest to report.

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