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Kidney Cancer

Depth of Remission is a Prognostic Factor for Survival in Patients with Metastatic Renal Cell Carcinoma

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Abstract

Background: Response remains an important endpoint in clinical cancer trials. However, the prognostic utility of best tumor response in metastatic renal cell carcinoma (mRCC) remains vague.
Objective: To define the prognostic relevance of the depth of remission in mRCC.
Design, setting, and participants: Pooled data from the Pfizer database for 2749 patients from phase 2 and 3 clinical trials in mRCC were analyzed. Tumor shrinkage was categorized according to the best percentage change in the sum of the largest diameter of target lesions. Outcome was computed using Kaplan-Meier curves and correlation was assessed via Cox regression, including a 6-mo landmark.
Intervention: Sunitinib, sorafenib, axitinib, temsirolimus, or temsirolimus and interferon-α.
Outcome measurements and statistical analysis: Categorized tumor shrinkage, overall survival (OS), progression free survival (PFS).
Results and limitations: Major tumor shrinkage of 60% or more occurred in approximately 10% of patients and was associated with median OS of 54.5 mo. OS expectations steadily decreased with depth of remission (26.4, 16.6, 10.4, and 7.3 mo). The association was maintained when stratified by type of therapy, line of therapy, and performance status. Cox proportional regression analyses for the 6-mo landmark confirmed the prognostic relevance of major tumor shrinkage (hazard ratio 0.29, 95% confidence interval 0.22–0.39; $p < 0.001$). The major limitation of our study is the variability of imaging intervals among studies.
Conclusions: This is the first and largest analysis of best tumor response in mRCC. We demonstrate that depth of remission is an independent prognostic factor in mRCC.
Patient summary: It remains unknown whether tumor shrinkage during therapy is needed to achieve clinical activity in metastatic renal cell carcinoma. Our analysis shows that the magnitude of tumor shrinkage correlates with better survival in patients. This observation may be used as a clinical research tool in future trials.
Trial registration: NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423, NCT00083889, NCT00065468, NCT00678392
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1. Introduction

Treatment of metastatic renal cell carcinoma (mRCC) has undergone a paradigm change in recent years. Targeted agents that inhibit vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) have replaced the previous standard of care, which consisted of cytokine treatment. A major criticism of these agents is their inability to induce complete or long-term remissions, a phenomenon that was a cornerstone for treatment outcomes in the cytokine era.

This field remained controversial because retrospective series indicated that complete remission (CR) and long-term response were possible in a fraction of patients with mRCC [1]. These data are supported by a recent analysis that underscored the ineffectiveness of objective response (OR) in predicting overall survival (OS) in mRCC treated with targeted agents [2,3]. More surprisingly, a minority of patients who achieved CR (2.7%) experienced superior OS estimates (63.2 mo), indicating that deep responses may benefit clinical outcome [2].

We hypothesized that deep tumor remission beyond the Response Evaluation Criteria in Solid Tumors (RECIST) 30% threshold for OR will provide prognostic relevance in mRCC. We therefore used a large contemporary clinical trials database containing data on mRCC patients treated with a broad range of therapies to characterize the significance of depth of remission in these patients.

2. Patients and methods

2.1. Study design

We conducted a pooled analysis of data from a clinical trials database including patients with mRCC treated in prospective phase 2 trials (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423) and phase 3 trials (NCT00083889, NCT00065468, NCT00678392) sponsored by Pfizer Oncology. We identified 2749 patients treated for mRCC between January 2003 and November 2011. Baseline demographic, clinical, and laboratory data were collected.

2.2. Imaging and imaging assessment

Patients underwent contrast-enhanced or non–contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis before therapy initiation and continued until disease progression or study withdrawal. Intervals for tumor assessment varied throughout the trials. Consecutive scans were performed after 4–8, 9–16, 16–24, 22–36, and 31–48 wk of therapy. Further tumor assessment in subsequent cycles was performed at 8–12-wk intervals. Measurements were performed prospectively by clinical investigators. Target lesions were selected in baseline imaging results according to RECIST version 1.0 [4]. For each baseline and follow-up imaging study, the longest axis of each target lesion was recorded to the nearest millimeter and the sum of the long-axis diameter (SLD) of target lesions was calculated. The percentage change in tumor burden was assessed at every available study time point. For each patient, the time point with the maximum tumor shrinkage in terms of percentage change in the SLD of target lesions was defined as the best response. Novel lesions were not assessed for tumor shrinkage.

2.3. Statistical methods

OS and progression-free survival (PFS), both prospectively assessed, were determined for the following tumor response categories: –100% to <–60%; –60% to <–30%; –30% to <0%; 0% to <+20%; ≥+20%; and patients without post-baseline imaging. Tumor response categories were prospectively defined based on an analysis of 100 mRCC patients [3]. The categories roughly correspond to RECIST response categories as follows: –100% to <–60% and –60% to <–30% correspond to CR and partial response (PR); –30% to <0% and 0% to <+20% correspond to stable disease (SD); and ≥+20% represents progressive disease (PD) [4]. We also tested whether tumor shrinkage cutoff parameters of ≥–10%, ≥-20%, and ≥-30% predict OS and PFS.

OS was defined as the time from therapy initiation (phase 2 studies) or randomization (phase 3 studies) to death from any cause. PFS was defined as the time from therapy initiation to date of progression or death from any cause, whichever came first. OS and PFS distributions were calculated using the Kaplan-Meier method. Median OS and PFS and the corresponding 95% confidence interval (CI) are reported. Associations between OS and PFS were assessed using the Cox proportional regression analysis, adjusted for age, sex, race, and the Memorial Sloan-Kettering Cancer Center (MSKCC) risk factors [5]. To correct for the potential bias of post-baseline factors, such as tumor shrinkage and confounding treatment effects, we also conducted a 6-mo landmark analysis. To explore whether subgroup analyses were justified, we performed an interaction analysis for tumor shrinkage (as a continuous covariate) and therapy type by applying a Cox regression model with a 6-mo landmark. Subgroup efficacy analyses were performed by: (1) line of therapy, (2) therapy type, and (3) performance status. The temsirolimus group included patients on temsirolimus or a combination of temsirolimus and interferon (IFN)-α.

3. Results

3.1. Patient and disease characteristics

Of the 2749 patients in the analysis, the majority were <65 yr of age and male, with good performance status and clear-cell histology (Table 1). Most patients underwent prior nephrectomy (84%) and 46% received prior therapy. Baseline lung and bone metastases were similar across categories; however, liver metastases were more frequent in the ≥+20% group.

Patients received treatment with sunitinib (n = 1059), sorafenib (n = 355), axitinib (n = 359), temsirolimus (n = 208), temsirolimus + IFN-α (n = 208), or IFN-α (n = 560), of whom 1759 received first-line therapy. The median baseline total tumor measurement was 103 mm/patient for the overall cohort. The most frequent response category was –30% to <0% (42%). Some 10% of patients had dramatic shrinkage (–100% to <–60%), most of whom (78%) were treated with axitinib, sorafenib, or sunitinib. A minority of patients (6%), 49% of whom received axitinib, sorafenib, or sunitinib, had ≥+20% growth as the best response. A total of 218 patients (8%) had no post-baseline imaging, most commonly because of disease progression (n = 77; 35%), adverse events (n = 61; 28%), or death (n = 43; 20%). When stratified by degree of tumor shrinkage, the median baseline tumor load was 70, 95, 114, 132, and 86 mm for the –100% to <–60%, –60% to <–30%, –30% to <0%, 0% to <+20%, and ≥+20% groups, respectively. For patients with no post-baseline imaging, the median

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