Original Study

The Effect of Targeted Therapy on Overall Survival in Advanced Renal Cancer: A Study of the National Surveillance Epidemiology and End Results Registry Database

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Abstract

Overall survival outcomes were compared before, and after availability of targeted therapy, in advanced RCC cases from the population-based SEER cancer registry. OS improved significantly in the advanced RCC patients treated in the targeted therapy (2005-2008) era as compared to the 2000-2003 time period. Increasing access to and optimizing targeted therapies will improve outcomes in advanced RCC

Introduction: With the advent and availability of targeted therapy, the treatment of advanced/metastatic renal cell carcinoma (RCC) underwent a drastic change in 2005. The effect of this change on clinical outcome within the population has not been studied. The aim of this study was to evaluate the overall survival (OS), before, and after availability of targeted therapy, for advanced RCC cases in the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registry. **Materials and Methods:** All advanced (regional and distant stage) RCC cases diagnosed within the 2000 to 2008 time periods were included. Because SEER does not report the exact therapy, and because targeted therapy was initially approved in 2005, we evaluated and compared the OS outcomes of advanced RCC cases diagnosed between the years 2000 and 2003 (before targeted therapy era) with that of those diagnosed between 2005 and 2008 (targeted therapy era). **Results:** There was a significant improvement in OS for advanced RCC patients treated in the targeted therapy era (n = 12,330) compared with those treated in the era before targeted therapy (n =11,565) (median OS 20 months vs. 15 months, $P = .0006$). Multivariate analysis revealed that in the time period before targeted therapy, age older than 65 years, black race, and lack of nephrectomy were predictors of a shorter OS. **Conclusion:** In univariate and multivariate analysis, targeted therapy demonstrated improvement in OS. Increasing access to targeted therapies is likely to improve outcomes in advanced RCC.

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Introduction

In the year 2013, an estimated 65,150 new kidney and renal pelvis cancers will be diagnosed in the United States and approximately 13,680 will die of the disease.[1] The predominant cause of mortality in kidney cancer is advanced or metastatic disease. Within the 2001 to 2007 time period, approximately 30% to 36% of patients with kidney and renal pelvis cancers had advanced stage disease (regional or metastatic disease) at initial presentation.[1] From 1990 to 2006 there has been a reported 6.8% absolute reduction in renal cell carcinoma (RCC) mortality.[2] Early detection of RCC in the localized stage, and increased rates of nephrectomy, are likely reasons for the decreased disease-related mortality in the localized stage. In advanced disease the most likely cause is the availability of better systemic therapies.

Before targeted therapy, immunotherapy[3,4] was the only systemic therapy indicated for advanced kidney cancer over the previous 2 decades. Targeted therapy based on the principle of vascular endothelial growth factor (VEGF) inhibition was approved by the Food and Drug Administration for routine use in 2005.[5-7] Subsequently, mammalian target of rapamycin (mTOR) pathway inhibition therapies were also approved.[8,9] These therapies demonstrated statistically

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significant progression-free survival benefit in randomized trials, and temsirolimus also demonstrated overall survival (OS) benefit. The availability of these agents changed the therapeutic dynamics in RCC, inducing a paradigm shift, from lack of effective therapy to that of tolerable and active therapy which is applicable to most RCC patients. However, outside of clinical trial data, the effect of these expensive and somewhat toxic therapies in a population-based sample of advanced RCC is unknown. The Surveillance, Epidemiology, and End Results (SEER) 17 cancer registry was thought to be the ideal database to explore this effect, because it is likely to reflect on the general population-based management of advanced RCC.

Materials and Methods

SEER Database

The National Cancer Institute's SEER program is a premier resource for cancer statistics in the United States. It collects information on cancer incidence and mortality from specific geographic and demographic areas representing 28% of the US population. The data collected include patient demographic characteristics, type of cancer, tumor characteristics, the extent of disease at time of diagnosis, and type of treatment received for the first course of therapy. Follow-up on each patient is conducted annually to assess current vital status.

All individuals diagnosed with regionally advanced (lymph node involvement) or metastatic clear-cell (CC) and non-CC RCC from January 1, 2000 to December 31, 2008 were included. Unknown race and autopsy/death certificate-only cases were excluded. Histologically confirmed RCC cases with regional/metastatic stage were selected, and data regarding patient demographic characteristics (sex, race, age), tumor histology, nephrectomy status, disease stage (regional/metastatic), initial therapy, and OS were collected. We restricted our study to the advanced RCC (regional and distant per SEER staging categories) cases only, and excluded localized disease cases, because systemic therapy is currently approved only in the locally advanced, unresectable, or metastatic stages of RCC.

Study Objectives

The primary objective of the study was to evaluate and compare the OS of regional and distant RCC cases diagnosed in the targeted therapy era with that of the era before targeted therapy. The exact type of therapy administered to the patient is not captured by the SEER registry. However, because targeted therapies became available only since the later part of 2005, we considered 2000 and 2003 as the era before targeted therapy and 2005 to 2008 as the targeted therapy era. We excluded the patients from the year 2004 to avoid overlap with any clinical trial population that might have received targeted therapy. The 2000 to 2003 and 2005 to 2008 time periods are hereinafter addressed as the "pre-targeted" and "targeted therapy" eras, respectively. We compared OS in both time periods and stratified according to sex (male, female), race (black, non-black), age (younger than 65, 65 years of age or older), stage (regional, distant), and nephrectomy status (yes, no).

The other objective was to evaluate the hazard ratio (HR) for risk of death in the targeted and pre-targeted time periods, when adjusted for the important demographic, disease-related, and treatment-related factors available in the SEER database such as, age, race, histology, stage, and nephrectomy.

Table 1 Baseline Patient Characteristics in the SEER 17 Registries

Variable	2000 to 2003 (n = 11,565), n (%)	2005 to 2008 (n = 12,330), n (%)
Median Age (Years)	66	66
Age Group		
< 65	5328 (46.1)	5803 (47.1)
≥ 65	6237 (53.9)	6527 (52.9)
Race		
White	9940 (85.9)	10461 (84.8)
Black	1035 (8.9)	1017 (8.3)
Other	569 (4.9)	814 (6.6)
Unknown	21 (0.2)	38 (0.3)
Stage		
Regional	5404 (46.7)	5902 (47.9)
Distant	6161 (53.3)	6428 (52.1)
Sex		
Female	3961 (34.3)	4055 (32.9)
Male	7604 (65.8)	8275 (67.1)
Histology		
Clear-cell	9296 (80.4)	9787 (79.4)
Non—clear-cell	2269 (19.6)	2543 (20.6)
Nephrectomy		
Yes	7063 (61.1)	7667 (62.2)
No	4502 (38.9)	4663 (37.8)

Abbreviation: SEER = Surveillance, Epidemiology, and End Results.

Statistical Analysis

Chi square test was used to compare the patient characteristics between the targeted and pre targeted therapy era. The Z test and Wilcoxon Mann-Whitney test, a nonparametric test, were used to compare the difference in the median ages between the time periods.

The Kaplan-Meier survival estimates method was used for generating the survival curves, and for computing the log-rank test and the survival proportions. Multivariate Cox proportional hazards models were used to assess the effects of prognostic factors, and estimate HRs of the different variables on OS, 95% confidence interval (CI), and P value.

Results

Patient Characteristics

In the SEER 17 data, 11,565 patients were diagnosed in the pre-targeted therapy era, and 12,330 patients in the targeted therapy era. No major differences in distribution of patient characteristics were identified between the 2 groups (Table 1). The median age was 66 years and most of the patients were white with black patients constituting approximately 8% of the population. Approximately two-thirds of the patients were men and the predominant histology was CC type (80%). Similar proportions of patients (approximately 60%) underwent nephrectomy in each of the time periods.

Overall Survival Data

In the targeted therapy era, advanced RCC cases (regional and distant disease) had a statistically significant improvement in OS than the pre-targeted therapy group ($P < .001$) (Fig. 1). The median OS