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Cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy in the United States: a SEER analysis

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Abstract

Purpose—Two randomized trials published in 2001 provided level 1 evidence for the use of cytoreductive nephrectomy (CyNx) for the treatment of metastatic renal cell carcinoma (mRCC). However, the regulatory approval of vascular endothelial growth factor tyrosine kinase inhibitors (VEGFR-TKI) in 2005 has left an “evidence void” regarding the use of CyNx. We evaluated the patterns in the use of CyNx in the cytokine and VEGFR-TKI eras, and the patient characteristics associated with the use of CyNx.

Methods—The Surveillance, Epidemiology, and End Results registry was used to identify patients with histologically or cytologically confirmed stage IV RCC between 2001 and 2008. Patients were classified as treated during the cytokine (2001–2005) or VEGFR-TKI (2006–2008) eras. A multivariate logistic regression analysis was performed to calculate the odds of undergoing CyNx according to treatment era and socioeconomic characteristics.

Results—Overall, 1,112 of 2,448 patients (45 %) underwent CyNx. CyNx use remained stable between 2001 and 2005 (50 %), but decreased to 38 % in 2008. Logistic regression analysis revealed that older age (OR 0.82, 95 % CI: 0.68, 0.99), black race (OR 0.64, 95 % CI: 0.46, 0.91), Hispanic ethnicity (OR 0.71, 95 % CI: 0.54, 0.93), and treatment in the VEGFR-TKI era (OR 0.82, 95 % CI: 0.68, 0.99) were independently associated with decreased use of CyNx.

Conclusions—Use of CyNx in the United States has declined in the VEGFR-TKI era. Older patients and minorities are less likely to receive CyNx. Results of ongoing phase III trials are needed to refine the role of this treatment modality.

Keywords

Cytoreductive nephrectomy; SEER; Targeted therapy; Tyrosine kinase inhibitor; Disparities

Introduction

Metastatic renal cell carcinoma (mRCC) has historically been treated with cytokine therapy [1]. Though resection of the primary tumor in the setting of distant metastatic disease was felt to play both a diagnostic and a potentially therapeutic role in the management of mRCC, this approach has not been without controversy [2, 3]. However, in 2001, two prospective, randomized trials (SWOG 8949 and EORTC 30947) demonstrated that use of cytoreductive nephrectomy (CyNx) in patients with mRCC treated with interferon-alpha 2b improved overall survival, establishing CyNx as a treatment standard [4, 5]. A pooled analysis of both of these trials reported a median survival of 13.6 months for nephrectomy plus interferon versus 7.8 months for interferon alone. CyNx was associated with a 31 % decrease in the risk of death ($p = 0.002$).

The use of CyNx had been steadily increasing after 2001, and was generally viewed as a treatment standard for surgical candidates, particularly without extensive metastatic disease burden [6]. However, with the Food and Drug Administration (FDA) approval of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) in 2005, a shift in the standard systemic therapy for mRCC created an “evidence void” regarding the utility of CyNx. The appropriateness of extrapolating the results of SWOG 8949 and EORTC 30947, to the era of VEGFR-TKIs, is unclear leaving clinicians uncertain of the appropriate role of CyNx. Given this recent change in existing level 1 evidence, it is important to examine ongoing changes in the patterns of modern day practice, as well as explore factors associated with the use of this treatment modality.

Material and methods

Patient cohort

Data for the current analysis were derived from the Surveillance, Epidemiology, and End Results (SEER) registry, which has collected clinical and pathological data on all incident cancer cases in specified geographic areas of the United States (US) since 1973, and are highly representative of the demographic makeup of the United States in terms of geography, socioeconomic status, race/ethnicity, and age. The 19 areas comprising the SEER registry represent approximately 26 % of the American population.

We identified patients diagnosed with histologically confirmed metastatic renal cell carcinoma (defined by confirmed metastases, local organ extension, or positive regional lymph nodes) diagnosed between years 2001 and 2008. Patients' baseline demographic data, year of surgery, and tumor characteristics were collected. The size of the primary tumor was clinically assessed based on radiographic imaging or pathologic specimens. CyNx was defined as surgical removal of a primary kidney tumor in the setting of mRCC. Patients who underwent radical nephrectomy, complete/total/simple nephrectomy, partial/subtotal nephrectomy, or kidney resection with other organ resection were included in the CyNx group. Only patients who did not undergo surgery were included in the “no surgery group.” Patients who had unknown surgical procedures, not otherwise specified procedures, or surgery on regional and/or distant sites only were excluded from the analysis. We selected 2001 as the initial year for analysis to coincide with publication of SWOG 8949 and EORTC 30947 and 2005 as the time of initial regulatory approval for VEGFR-TKI's use in renal carcinoma [4, 5]. We used 2001–2005 and 2006–2008 as a proxy for the cytokine and VEGFR-TKI eras, respectively.

Statistical analyses

The baseline differences in demographic characteristics of patients treated with and without CyNx were compared using the χ^2 and t test for categorical and continuous variables, respectively. The trend in prevalence rates of CyNx over time was then analyzed using a modified poisson regression model with linear, quadratic, and cubic terms for time. The highest order term that was significant was the cubic term for time so that term and both lower order terms were retained in the final model, and a 3 df test for overall trend was computed. A multivariate modified Poisson regression model was utilized to estimate

prevalence ratios to assess whether the VEGFR-TKI era, and other factors were independently associated with CyNx use. Because tumor size was missing for 436 patients, only 2012 of 2448 cases were included in the final adjusted analysis. Models were run both with and without adjustment for tumor size, and each of the prevalence ratios and their corresponding standard errors for any of the other covariates in the model were not changed with statistical significance. All analyses were performed using the Statistical Analysis Software (SAS) program, version 9.2 (SAS Institute, Cary, NC) and Statistical Package for the Social Sciences (SPSS), version 19 (IBM, Armonk, NY).

Results

The baseline patient characteristics are detailed in Table 1. A total of 2,470 patients diagnosed with stage IV RCC between years 2001 and 2008 were identified in the SEER database. We excluded 22 patients who had unknown or unspecified surgeries or who underwent excisional biopsies. Of the 2,448 remaining patients, 1,112 patients (45.4 %) underwent CyNx. The prevalence of undergoing CyNx in this analysis is detailed in Table 2. Patients who underwent CyNx were significantly younger than patients who did not undergo surgery (59.8 vs. 65.4 years, $p < 0.001$). In addition, patients who underwent CyNx were more commonly white (74 % vs. 69 %, $p = 0.097$) and married (67 vs. 55 %, $p < 0.001$). CyNx treated patients had slightly smaller primary tumors compared with patients not undergoing surgery (93.2 vs. 84.4 mm, $p < 0.001$).

The prevalence of CyNx use varied during the study period. In 2001, 49 % of patients with stage IV RCC underwent CyNx, which remained stable to 2005 when 50 % underwent CyNx. Subsequently, the rate decreased to 38 % in 2008 (Fig. 1). On univariate analysis, there was a 10 % decreased prevalence of undergoing CyNx in the VEGFR-TKI era compared to the cytokine era (prevalence ratio [PR] 0.90, 95 % confidence interval [CI] 0.82, 0.99).

The results of the multiple regression analysis are shown in Table 2. After controlling for demographic and tumor characteristics, there was a 9 % decreased prevalence of undergoing CyNx in the VEGFR-TKI era (PR: 0.91; CI: 0.84, 0.99). With every 10-year increase in age, the prevalence of undergoing CyNx decreased by 16 % (PR: 0.84; 95 % CI: 0.81, 0.87). Blacks were 18 % less likely (PR: 0.82; 95 % CI: 0.69, 0.97) and Hispanics were 14 % less likely (PR: 0.86, 95 % CI: 0.76, 0.97) than Caucasians to undergo CyNx. Compared to patients who were not married, married patients were 25 % more likely to undergo CyNx (PR: 1.25, 95 % CI: 1.15, 1.37). Patients with larger tumors had increased prevalence of undergoing cytoreductive nephrectomy by 2 % for every additional 20 mm of tumor size (PR: 1.02, 95 % CI: 1.01, 1.03). Finally, there was no significant difference between gender in the use of CyNx (PR: 0.96; 95 % CI: 0.88, 1.05).

Discussion

The shift in the first-line treatment paradigm for metastatic RCC, from cytokines to VEGFR-TKIs, has resulted in an “evidence void” regarding the role of CyNx. In a previous study using the National Cancer Database (NCDB), a hospital-based cancer registry jointly

sponsored by the American College of Surgeons and the American Cancer Society which represents over 75 % of all new cancer diagnoses in the United States, we found that the use of CyNx in patients with metastatic RCC has been decreasing since the FDA approval of VEGFR-TKIs in 2005 [7]. In addition, we identified several socioeconomic factors potentially associated with decreased application of CyNx. However, our prior study was limited in that only aggregate patient data were available, precluding multivariate analysis to determine which of several seemingly related variables were independently associated with a lower likelihood of undergoing CyNx. In the current analysis, with individual patient level data from SEER, we have confirmed and expanded our prior findings.

The current analysis reveals that the application of CyNx has declined since the approval of VEGFR-TKIs. This trend is not surprising, given the uncertainty regarding the utility of CyNx in the age of VEGFR-TKIs, and concerns for potentially delaying effective systemic therapy [8]. Two ongoing randomized phase III studies are expected to generate definitive evidence to guide the optimal use and timing of CyNx in the setting of newer generation systemic therapies [9]. CARMENA (NCT00930033) is a randomized phase III study comparing CyNx plus sunitinib to treatment with sunitinib alone in patients with mRCC with a primary endpoint of overall survival. A randomized phase III conducted by the European Organization of Research and Treatment of Cancer (NCT01099423) is comparing immediate versus deferred CyNx in patients with mRCC with a primary endpoint of progression-free survival. These trials are expected to be completed in 2013 and 2014, respectively.

In addition to differences in the application of CyNx based on the ‘era’ of treatment, the current analysis also suggests that patient demographics were associated with the use of CyNx. Increasing age was associated with a decreased likelihood of CyNx. This finding was not unexpected, given concerns for increased operative morbidity and mortality in the elderly, particularly in the setting of an incurable malignancy [10]. Perhaps more concerning were the potential differences observed based on race, ethnicity, and marital status. Black and Hispanic patients were significantly less likely to undergo CyNx compared with Caucasians. While underlying biology of the disease may play a role [11, 12], decreased accessibility and/or acceptability of CyNx is likely a more plausible explanation. Several studies have demonstrated decreased accessibility, and/or acceptability, of a variety of therapeutic modalities in racial/ethnic minority populations with other solid tumors [13, 14]. Marital status was also shown to be independently associated with undergoing CyNx in the current analysis, with married patients 59 % more likely to undergo surgery. Marital status has been regarded as an important surrogate for social support [15], and previous studies have also described an association between marital status and the likelihood of undergoing CyNx [16, 17].

Another interesting finding is that patients with larger tumors actually had increased odds of undergoing CyNx by 0.4 % per additional millimeter of tumor size. While speculative, this may be a result of an increased likelihood of symptoms associated with larger primary tumors, or at least the threat of impending morbidity, resulting in increased acceptance of CyNx by both the patient and urologist.

The current analysis has several potential strengths. SEER represents 18–26 % of the cancer population in the United States. Geographic regions included in SEER encompass varying levels of urbanization, income strata and education, mirroring the diversity of the greater United States population. Furthermore, the years encompassed by the SEER data include the time period when randomized trials both established the utility of CyNx and subsequently altered the systemic therapy landscape for renal carcinoma.

There are also several important limitations to the current analysis. First, and foremost, details regarding the specific systemic therapies administered were not available, and instead, we categorized cytokine and VEGFR-TKI eras based on the timing of initial regulatory approval of the VEGFR-TKIs. Second, data regarding co-morbidities and performance status were not ascertained, potential confounding factors regarding the use of cytoreductive nephrectomy. Third, limited by the data available in our study using the SEER database, the VEGF-TKI era is limited to years 2006–2008, and factors such as histological subtype, prognostic scores, treatment type, and length of treatment were not available for the analysis. Fourth, SEER data are limited to the United States, and the racial and socioeconomic disparities that were observed in the current analysis may not exist in other countries.

The role of CyNx in the management of mRCC in the VEGFR-TKI era is in evolution. Despite the lack of level 1 evidence, many still consider CyNx the default standard approach in appropriate surgical candidates, given the both diagnostic, and potential therapeutic, role of this treatment modality. Several retrospective studies have explored the role of CyNx in the VEGFR-TKI era and have suggested that the surgery is safe and may be associated with improved clinical outcomes [8, 18–23]. To our knowledge, our study is the first to evaluate changes in the patterns of use of this modality in the cytokine versus VEGFR-TKI eras and supports the suspected general uncertainty regarding the appropriate integration of surgery in the age of targeted therapeutics. While we also identified potential racial, ethnic, and socioeconomic differences in the application of CyNx, the lack of a definitive role for CyNx in the current era limits the extent to which these differences can be considered inappropriate. Nonetheless, systematic differences in the application of a therapeutic modality for the treatment of cancer based on such factors remain concerning. The results of ongoing randomized trials evaluating the role of CyNx in the VEGFR-TKI era are awaited in an effort to optimize use of this treatment modality and to address barriers to accessibility and acceptability should CyNx be proven beneficial.

Conflict of interest

Dr. Sonpavde receives research support from Pfizer and is an ad board/speaker for Pfizer, Novartis, and Glaxo-KlineSmith. Dr. Wisnivesky is a member of the research board of EHE International, has been a consultant for UBS and IMS Health, and received a research grant from GlaxoSmithKline.

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Fig. 1.
The use of CyNx in the United States, 2001–2008 (SEER database). There is a significant cubic trend in CyNx over time; $p = 0.0041$

Table 1

Baseline characteristics of patients undergoing cytoreductive nephrectomy or no surgery for stage IV RCC

Characteristic	CyNx <i>N</i> = 1112	No CyNx <i>N</i> = 1336	<i>p</i> value
Age (years), mean ± SD	59.8 ± 11.1	65.4 ± 12.8	<0.001
Female sex, <i>N</i> (%)	342 (31)	478 (36)	0.009
Race/ethnicity, <i>N</i> (%)			0.097
White	820 (74)	924 (69)	
Black	80 (7)	117 (9)	
Hispanic	140 (13)	193 (14)	
Other	72 (7)	102 (8)	
Married, <i>N</i> (%)	744 (67)	739 (55)	<0.001
Tumor size (mm), mean ± SD	93.2 ± 51.8	84.4 ± 40.7	<0.001
Era of diagnosis, <i>N</i> (%)			0.022
Cytokine (2001–2005)	703 (63)	784 (59)	
VEGFR-TKI (2006–2008)	409 (37)	552 (41)	
Surgical procedure, <i>N</i> (%)			–
Partial Nx or tumor destruction	38 (3)	–	
Complete/total/simple Nx	66 (6)	–	
Radical Nx	926 (83)	–	
Nx plus other resection or NOS	84 (8)	–	

Bold values indicate the significance of *p* value <0.05

Table 2

Prevalence ratios comparing probabilities of undergoing CyNx for stage IV RCC using the modified Poisson regression model

Characteristic	PR	95 % CI	<i>p</i> value
Age (10 years)	0.84	[0.81, 0.87]	<0.0001
Female sex (vs. male)	0.96	[0.88, 1.05]	0.4184
Race/ethnicity			
Black (vs. White)	0.82	[0.69, 0.97]	0.0216
Hispanic (vs. White)	0.86	[0.76, 0.97]	0.0163
Other (vs. White)	0.89	[0.75, 1.06]	0.1975
Married (vs. not married)	1.25	[1.15, 1.37]	<0.0001
Tumor size (20 mm)	1.02	[1.01, 1.03]	<0.0001
VEGFR-TKI era (2006–2008) (vs. Cytokine era)	0.91	[0.84, 0.99]	0.0322

Bold values indicate the significance of *p* value <0.05