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Original article

An evaluation of race, ethnicity, age, and sex-based representation in phase I to II renal cell carcinoma clinical trials in the United States

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Abstract

Introduction: Enrollment of a representative study population permits generalizable and reliable results for clinical trials. We sought to evaluate whether patients enrolled in trials for advanced renal cell carcinoma (RCC) are representative of the overall population of advanced RCC patients in the United States.

Materials and methods: The clinicaltrials.gov results database was queried for interventional clinical trials directed at clinically advanced (stage III/IV) RCC that enrolled patients from the US only. We identified 375 patients from 18 phase I to II trials that met eligibility criteria. The American College of Surgeons' National Cancer Database (NCDB) which includes data on approximately 70% of all US cancer diagnoses was queried and we identified 75,308 patients with advanced (stage III/IV) RCC. Demographic characteristics were summarized and compared between the 2 populations.

Results: Compared to the US population of advanced RCC (NCDB), significant under-representation in clinical trials was observed for patients aged 65+ (26.3% vs. 50.4%; $P < 0.001$) and among those with Hispanic ethnicity (2.7% vs. 7.2%; $P = 0.005$). A trend toward under-representation was observed for black patients (7.0% vs. 9.8%, $P = 0.076$) but not for white patients (89.9% vs. 87.0%, $P = 0.107$) or other racial groups ($P > 0.05$ for all). Female patients made up 30.3% of trial enrollees and 33.3% of the US advanced RCC population ($P = 0.221$).

Conclusion: Significant under-representation was observed for elderly and Hispanic patients with a trend toward under-representation for black and female patients in phase I to II RCC clinical trials. Greater efforts to include underrepresented populations are necessary to improve the effectiveness and generalizability of clinical trials in kidney cancer. © 2018 Published by Elsevier Inc.

Keywords: Renal cell carcinoma; Clinical trials; Demographics; Participation; Generalizability

1. Introduction

A key objective in designing a clinical trial is to ensure that if the experimental treatment is proven to be successful in the study group, then it will also be successful in the population at large. This concept, first introduced by Campbell in 1957, is known as external validity, or generalizability [1]. Generalizability is dependent on numerous factors, including trial setting, patient selection, and patient characteristics, all of which should be considered when determining potential effectiveness of a treatment in the target population [2] Despite efforts by governing bodies and trial designers to create study populations representative of the target population, generalizability of cancer clinical trials remains challenging, particularly when considering that fewer than 5% of cancer patients enroll in clinical trials [3–5]. In the US, this percentage is even lower among minorities compared to white patients [5].

With the passage of the National Institutes of Health (NIH) Revitalization Act of 1993, all NIH-funded clinical trials are required by law to include women and racial and ethnic minority groups [6]. Still, the vast majority of clinical trials and randomized controlled studies in high-impact journals do not report results by race, ethnicity, or sex [7,8]. In fact, most peer-reviewed research is derived from

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predominantly white and male populations [9]. This, however, has not been explored in renal cell carcinoma (RCC) that has a higher incidence among black compared to white Americans [10,11]. We therefore sought to evaluate whether the population of patients enrolled in trials for advanced RCC in the US is representative of the overall population of advanced RCC patients in the United States.

2. Materials and methods

2.1. Clinicaltrials.gov results database population

We queried the clinicaltrials.gov results database for terminated or completed interventional studies with results, using the search term "renal cell carcinoma." Our search included adult (18–65) and senior (66+) age groups, all sexes, and trials of all phases. Trials were reviewed and excluded if they did not include data on race, or if they enrolled patients from outside of the United States. Trials were also excluded if they were not directed at clinically advanced (pathologic stage III/IV) RCC alone, as systemic therapy has clinical applications only in advanced RCC. Our initial query of clinicaltrials.gov returned 177 clinical trials; 80 of which were excluded for targeting conditions other than clinically advanced RCC alone. An additional 73 trials were excluded that did not include data on race with an additional 4 excluded that enrolled patients from outside of the United States and an additional 2 trials excluded that were noninterventional. There were 18 clinical trials that met eligibility criteria and included data on 375 patients enrolled in phase I to II clinical trials. No phase III clinical trials met eligibility criteria.

2.2. National Cancer Database population

The American College of Surgeons' National Cancer Database was utilized to identify 390,884 patients with diagnosed stage III or IV kidney cancer from 2004 to 2014. The NCDB is a collaborative project of the American College of Surgeons and the American Cancer Society and contains patient-level and hospital-level data from 1,500 Commission on Cancer hospitals, including an estimated 70% of all new cancer diagnoses in the United States [12]. Patients with clinical stage III to IV RCC were included. Therefore 310,902 patients with clinical stage I to II RCC or missing stage data were excluded and 4,674 patients with non-RCC histology were excluded. There were 75,308 patients with stage III-IV RCC that met eligibility criteria.

2.3. Statistical analysis

Our primary outcome was the difference in the proportion of racial groups in United States clinical trials of advanced (stage III–IV) RCC (clinicaltrials.gov database) compared to the proportion of racial groups in the general US population of patients with advanced (stage III–IV) kidney cancer (NCDB database). Our secondary outcome was the difference in representation of age, sex, and ethnic groups between these 2 populations. Racial groups were categorized in the database as White, Black, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or Other. Age was treated categorically as <65 vs. 65+ and ethnicity was classified as Hispanic vs. non-Hispanic. The distributions of race, age, sex, and ethnicity were compared between groups with chi-squared tests of independence or Fisher exact tests with statistical significance considered at the $P < 0.05$ level. All analysis was conducted using R version 3.3.1.

3. Results

Study details of the 18 included clinical trials are presented in Table 1. Complete demographic characteristics of both the U.S. RCC clinical trial enrollees ($n = 375$) and U.S. RCC patients ($n = 75{,}308$) are presented in Table 2.

Compared to the US population of advanced RCC (NCDB), we did not find a large disparity between black and white patients; there was a trend toward under-representation in clinical trials for black patients (7.0% vs. 9.8%, $P = 0.076$) with a trend toward over-representation of white patients (89.9% vs. 87.0%, $P = 0.107$). Representation for other racial groups was relatively equivalent with rates of representation in the clinical trials and US advanced RCC population being 2.2% vs. 1.7% ($P = 0.426$) for Asian patients, 0.3% vs. 0.1% ($P = 0.365$) for Native Hawaiian, or Other Pacific Islander patients, 0.0% vs. 0.6% ($P = 0.181$) for American Indian or Alaska Native patients and 0.6% vs. 0.7% ($P < 0.999$) for individuals of other races, respectively.

Under-representation in clinical trials was observed for patients of Hispanic ethnicity making up 2.7% of clinical trial enrollees but 7.2% of the US population of advanced RCC ($P = 0.005$). Under-representation in clinical trials was also observed for patients aged 65 years or older making up only 26.3% of clinical trial enrollees but 50.4% of the US population of advanced RCC ($P < 0.001$). Furthermore, female patients made up 33.3% of the US population of advanced RCC but only 30.3% of clinical trial patients, showing a trend toward under-representation of females in US clinical trials ($P = 0.221$).

4. Discussion

The present study demonstrates significant under-representation of elderly and Hispanic patients with a trend toward under-representation for black patients and female patients in phase I to II RCC clinical trials. Disproportionate representation of minority groups in clinical trials has significant adverse implications for patient outcomes. Specifically, under-representation of sub-populations decreases