Review

Acquired Hypothyroidism as a Predictive Marker of Outcome in Patients With Metastatic Renal Cell Carcinoma Treated With Tyrosine Kinase Inhibitors: A Literature-Based Meta-Analysis

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Abstract

Hypothyroidism in patients with metastatic renal cell carcinoma (mRCC) during treatment with the tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib is a well-established side effect. Furthermore, the potential role of hypothyroidism as predictive marker of outcome has been studied but with conflicting results. The aim of the present meta-analysis was to assess the predictive value of hypothyroidism for progression-free (PFS) and overall survival (OS) in patients with mRCC during TKI therapy. We searched PubMed and the electronic abstract databases of the major international congresses' proceedings to identify all eligible studies that reported a correlation between the development of hypothyroidism during TKI treatment and outcome in patients with mRCC. Hazard ratios (HRs) with 95% confidence intervals (CIs) for PFS and OS were obtained from these publications and pooled in a meta-analysis. Eleven studies with a total of 500 patients fulfilled the inclusion criteria. We found no statistical significant difference in PFS between patients who developed hypothyroidism during sunitinib therapy and unaffected patients (HR, 0.82; 95% CI, 0.59-1.13; $P = .22$; 6 studies; 250 patients). The HR for OS was 0.52 (95% CI, 0.31-0.87; $P = .01$) for patients who developed hypothyroidism during sunitinib therapy compared with patients who did not (4 studies; 147 patients). The development of hypothyroidism during TKI therapy is not clearly shown to be predictive of efficacy in patients with mRCC. The observed advantage in OS for the patients with acquired hypothyroidism should be interpreted with caution.

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 90% of all renal malignancies.[1] Approximately 20% to 30% of all new RCC patients are diagnosed with metastatic disease. In addition, another 40% of surgically treated patients will have a relapse and develop metastatic RCC (mRCC) during follow-up.[2]

Historically, the prognosis of patients with mRCC was extremely poor and the therapeutic options limited. However, presently 7 different molecular targeted therapies (either targeting the Vascular Endothelial Growth Factor/Vascular Endothelial Growth Factor Receptor or the mammalian target of rapamycin [mTOR] pathway) have been approved for the treatment of mRCC.[3-8] In this new era of targeted therapies, the median survival for patients with mRCC has been extended to 30 to 36 months.[9-11] The oncologists are facing a challenge in treatment decision-making for patients with mRCC because there are 4 alternatives as first-line treatment and 3 more that serve as second- or third-line therapies. During the past years, many investigators have therefore tried to find predictive factors that could help the treating physicians choose the most ideal sequence of targeted therapies for each individual.[12-18] Currently there is, however, no clear consensus about the sequence of targeted therapies and the efforts to identify factors that predict outcome for each treatment option continue.

The tyrosine kinase inhibitors (TKIs) are designed to selectively inhibit the enzymes that are responsible for the signal transduction

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cascades. In addition to their beneficial antitumor activity, clinical toxicities have also been observed. These might be caused by multiple so-called "off-target" effects and downstream signaling pathways of target kinases.[19] A potential side effect of TKIs, the pathophysiological mechanism of which has not yet been completely explained, is the development of hypothyroidism. Specifically, sunitinib and sorafenib have been associated with the development of hypothyroidism.[20] Several studies have found that some drug-specific toxicities of targeted therapies might serve as predictive factors for treatment efficacy.[21] A similar hypothesis that the development of hypothyroidism during the treatment of mRCC with sunitinib or sorafenib could predict treatment efficacy has been proposed. Several investigators have studied this hypothesis but their results are conflicting.

Because of the large spectrum of treatment alternatives and the increasing need for predictive markers, we conducted a meta-analysis of relevant studies to determine whether acquired hypothyroidism during TKI therapy can serve as a predictive marker of efficacy in patients with mRCC.

Materials and Methods

Search Strategy

Two independent investigators (AN and AV) searched the PubMed and the electronic abstract databases of the major international congresses' proceedings (the American Society of Clinical Oncology [ASCO] Annual Meeting, the ASCO Genitourinary Cancers Symposium, and the European Society for Medical Oncology [ESMO] congresses) using the following searching algorithm: (sunitinib OR sorafenib OR pazopanib OR axitinib) AND renal cancer AND hypothyroidism. There were no restrictions on the language or the year of publication and the search was updated in June 2014. Furthermore, all reference lists of eligible studies and relevant reviews were also scrutinized to identify relevant articles missed by the electronic searches.

When more than 1 publication was identified from the same study, we used the report with the longest follow-up or with the largest cohort to avoid duplication of results.

Selection Criteria

The studies were considered eligible if they included patients with mRCC who were treated with TKIs and reported rates of acquired hypothyroidism and efficacy data. We excluded studies that included patients with different types of cancer and studies that did not provide any efficacy data on patients with euthyroidism versus hypothyroidism. We also excluded case reports.

Data Extraction

Two independent authors (AN and AV) extracted the data from the studies and consensus was achieved in all the cases. From each study we extracted the following information (in a prespecified form): author names, year and journal of publication, country of origin, type of study (prospective or retrospective), the definition of hypothyroidism as stated by the authors; type of TKIs given, previous treatment, treatment setting; number of eligible and analyzed patients, sex, age; median follow-up; number of patients with acquired hypothyroidism and time to development of hypothyroidism; outcome measures (as described herein); type of analysis used in each outcome (bivariate or multivariate), and variables in multivariate analysis.

In case of lack of data, we contacted the primary investigators of each study to provide us with supplementary data.

Risk of Bias and Publication Bias

Two authors (AN and AV) independently assessed the risk of bias in each eligible study using the Newcastle−Ottawa (NOS) quality assessment scale for cohort studies. The NOS ranges between 0 and 9 stars, with the highest quality studies awarded with a maximum of 9 stars.

Publication bias was assessed using the construction of contour-enhanced funnel plots.

Outcome Measures

The primary outcome of the meta-analysis was the progression-free survival (PFS) difference between patients who developed hypothyroidism during TKI therapy versus euthyroid patients. The definition of PFS was equal among studies and defined as time from initiation of TKI therapy to disease progression or death (except from 1; Shinohara et al[22]). The secondary end point was difference in overall survival (OS; defined as time from initiation of TKI therapy to death from any cause).

Statistical Analysis

Meta-analyses were performed only if more than 2 studies presented adequate data for the outcome of interest.

For the time to event outcomes (PFS and OS), we performed a meta-analysis first by transforming the hazard ratio (HR) and their errors into their log counterparts, and then by using the inverse of variance method and then transformed back into the HR scale. In case of inadequate data (lack of HR with confidence intervals [CIs]) we calculated the HR by using the Kaplan−Meier curves or log-rank P values and the number of events and total number of patients according to the method described by Tierney et al.[23] We assessed the presence of statistical heterogeneity among the studies using the Q statistic and the magnitude of heterogeneity by using the I^2 statistic. We considered $P < .10$ or an $I^2 > 50\%$ as indicative of substantial heterogeneity. In case of substantial heterogeneity, the pooled odds ratio was calculated based on the random-effects model by DerSimonian and Laird.[24] Otherwise, the fixed-effects model with the Mantel−Haenszel method was used.

Subgroup analyses were performed based on type of study (prospective vs. retrospective), type of treatment used (sunitinib, sorafenib, and sunitinib or sorafenib). All data used in the meta-analyses were derived from bivariate analyses because of the lack of data from multivariate analyses.

All reported P values are 2-sided, with significance set at $P < .05$. All statistical analyses were performed using the Review Manager software (version 5.0; The Nordic Cochrane Centre, The Cochrane Collaboration).

Results

Study Selection

Our initial search identified a total of 67 potentially relevant studies in PubMed and 5 relevant trials in the ASCO and ESMO online databases. Of these, 46 were excluded leading to 26