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Adjuvant Antiangiogenic Agents in Post-nephrectomy Renal Cell Carcinoma: A Systematic Review and Meta-analysis

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Abstract

Context: The role of antiangiogenic agents in advanced renal cell carcinoma (RCC) is well established. However, it is still not clear whether this benefit can be extrapolated to the adjuvant setting.

Objective: To determine the efficacy and safety of antiangiogenic agents in patients with RCC and a high risk of relapse after nephrectomy.

Evidence acquisition: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) evaluating the use of any oral antiangiogenic agent compared to placebo in post-nephrectomy RCC patients. Prespecified data elements were extracted from each trial. Outcomes of interest included overall survival (OS) and disease-free survival (DFS). The overall effect was pooled using the DerSimonian and Laird random-effects models.

Evidence synthesis: Three RCTs comparing antiangiogenics to placebo among 3693 patients met our inclusion criteria and were used in meta-analyses. Overall, antiangiogenics did not improve DFS (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.78–1.07) or OS (HR 0.99, 95% CI 0.79–1.25). These results persisted when restricting the analysis to patients with clear cell carcinoma and patients with highest risk of relapse. Similarly, sunitinib did not show any improvement in the entire cohort for either DFS (HR 0.89, 95% CI 0.67–1.19) or OS (HR 1.11, 95% CI 0.90–1.37).

Conclusions: In this meta-analysis, antiangiogenics did not improve OS and DFS over placebo in high-risk RCC after nephrectomy. Further studies are needed to identify the patient population that might derive a benefit from antiangiogenics in the adjuvant setting.

Patient summary: In this article, we found that there is currently insufficient evidence to support the use of oral antiangiogenics in nonmetastatic renal cell carcinoma after nephrectomy. In addition, the use of oral antiangiogenics was associated with a 2.7-fold higher rate of significant side effects compared to placebo.

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1. Introduction

Each year, there are approximately 64 000 new cases of renal cell carcinoma (RCC) in the USA, and 14 000 deaths [1]. Clear-cell histology is the most common histology, accounting for 75–80% of all RCC cases. Surgical resection with nephrectomy has been the standard of care for nonmetastatic RCC, with close surveillance afterwards. However, despite surgical resection, approximately one-third of patients experience relapse [2]. Given their efficacy and survival benefit in the metastatic RCC setting, antiangiogenics, also known as VEGF tyrosine kinase inhibitors (TKIs), have been studied in the adjuvant setting to evaluate their efficacy in potentially decreasing the rate of relapse and enhancing cure. Several trials utilizing different VEGF TKIs have been completed and reported conflicting results [3–7].

In this meta-analysis, we sought to determine the efficacy and safety of adjuvant VEGF TKIs in patients with RCC who are at high risk of relapse after nephrectomy.

2. Evidence acquisition

The reporting of this systematic review follows the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [8].

2.1. Study eligibility

We included randomized controlled trials (RCTs). The search was not limited by language, sample size, or date of publication. We searched for studies that included patients with nonmetastatic RCC who underwent nephrectomy and afterwards received either a VEGF TKI or placebo in the adjuvant setting. Outcomes of interest were disease-free survival (DFS), overall survival (OS), and grade $\geq$3 toxicities.

2.2. Information sources and search methods

A comprehensive literature search was conducted from database inception through January 1, 2018 for the electronic databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant abstracts and titles. The detailed search strategy is described in the Supplementary material. Two individual reviewers (M.B.S. and T.H.) identified articles that were eligible for further review by screening the available abstracts and titles. If a study was deemed relevant, then it was obtained and reviewed. Disagreements were harmonized via consensus and through arbitration by a third reviewer if consensus was not possible. The final search identified five articles reporting three RCTs (Supplementary Fig. 1).

2.3. Data collection and extraction

Prespecified data elements were extracted from each trial, including baseline characteristics, study design, sample size, interventions used, outcome measures, funding sources, pathological features, and adverse events (Table 1) [3–7]. Two reviewers extracted the data from the included studies, and disagreements were resolved by referring to a third reviewer. The number of events in each trial was extracted, when available, based on the intention-to-treat approach.

2.4. Risk of bias assessment and quality of evidence

We used the Cochrane Collaboration risk of bias assessment tool for randomized trials, focusing on randomization methods, allocation concealment, blinding, and attrition [9].

2.5. Statistical analysis

Analyses were conducted using features on RevMan version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). We used the hazard ratio (HR) provided by the included trials to conduct a pooled HR for survival outcomes. We conducted random-effects meta-analyses using the DerSimonian and Laird method to pool treatment effects from included studies [10]. We used the I^2 statistic to assess for heterogeneity across the included studies. An I^2 value $>$50% suggests substantial heterogeneity between studies. Two-sided p values $<$0.05 suggest statistical significance. We conducted sensitivity analyses using leave-one-out meta-analyses to assess the influence of each study on the overall results.

3. Evidence synthesis

3.1. Search strategy

In total, 1251 titles and abstracts were identified via the screening electronic strategy, of which five articles describing three RCTs met the inclusion criteria evaluating the use of VEGF TKIs versus placebo in post-nephrectomy RCC patients (Supplementary Fig. 1). The main reasons for exclusions were: the use of different medications in the adjuvant setting; the use of adjuvant VEGF TKIs in other malignancies; and nonrandomized controlled trials (mainly reviews). The three RCTs included a total of 3693 enrolled patients (Table 1).

3.2. Trial characteristics

The first study was the ASSURE trial (we will refer to this in the text as ASSURE 2016), which is a multicenter, phase 3 clinical trial in the USA and Canada, led by the Eastern Cooperative Oncology Group (ECOG-ACRIN) with participation by multiple other cooperative groups [7]. The study assessed the use of sunitinib or sorafenib compared to placebo in patients with nonmetastatic RCC post-nephrectomy (n = 1943) with node-positive (N+) or pT1b G3–4 N0 M0 disease (Table 1). Both clear cell and non-clear cell histologies were included. Patients received 1 yr of adjuvant sunitinib (50 mg), sorafenib (800 mg), or placebo. However,