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A systematic review of predictive and prognostic biomarkers for VEGF-targeted therapy in renal cell carcinoma

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ABSTRACT

Background: Vascular endothelial growth factor (VEGF)-targeted therapy is the currently standard treatment for advanced and metastatic renal cell carcinoma (RCC). Multiple candidate predictive and prognostic biomarkers have been evaluated. We performed a systematic review and graded the available evidence on the biomarkers for VEGF-targeted therapy in RCC.

Methods: We conducted an independent review of PubMed and ASCO databases up to August 2013. Studies were included if biomarkers obtained from metastatic clear-cell RCC patients treated with the FDA-approved VEGF-targeted therapy were assessed for their correlation with clinical outcomes. We graded the studies and determined the Level-of-evidence for each biomarker using a previously published framework.

Results: A total of 50 articles were selected for this review. Seven studies assessed the predictive value of biomarkers using the archived specimens from randomized controlled trials. Five predictive biomarkers, such as VEGF, interleukin (IL)-6, hepatocyte growth factor (HGF), osteopontin, single nucleotide polymorphisms in IL-8, satisfied Level II evidence. IL-6 is the most corroborated predictive biomarker based on its consistent predictive value in two different trials. The prognostic value of biomarkers was assessed in 48 studies using the archived specimens from clinical trials, prospective and retrospective observational registries. Three biomarkers, including IL-8, HGF and osteopontin, satisfied Level I evidence for PFS.

Conclusion: Though several promising predictive biomarkers for VEGF-targeted therapy have been found, none of them has satisfied the determination of Level I evidence. A more focused development of biomarkers with prospective assessment in clinical trials and clear intent of use in clinical practice is needed.

Introduction

Clear-cell renal cell carcinoma (RCC) is refractory to cytotoxic chemotherapy. Until recently, interleukin 2 (IL-2) and interferon (IFN) were the standard of care for advanced and metastatic clear-cell RCC, even though they only benefit a small portion of patients at the expense of substantial toxicity. The elucidation of the von Hippel-Lindau (VHL) pathway has led to the development of therapy targeted at specific molecular alterations. VHL gene inactivation, which occurs in the majority of sporadic clear cell RCC, results in accumulation of hypoxia-inducible factor (HIF) alpha subunits, which causes downstream upregulation of a number of pro-angiogenic factors, including the vascular endothelial growth factor (VEGF) [1]. This led to the development of VEGF signaling pathway inhibitors which have been shown to benefit patients in randomized phase III clinical trials. Currently, there are five angiogenesis inhibitors approved by the United States Food and Drug Administration (FDA) for treatment of advanced and metastatic RCC; four VEGFR targeted tyrosine kinase inhibitors (TKIs), including sorafenib, sunitinib, axitinib and pazopanib, and one anti-VEGF monoclonal antibody, bevacizumab [2–6].

Despite the improved outcomes shown in the clinical trials of VEGF-targeted therapy, the length of response and survival benefit of therapy varies considerably between patients. In addition, VEGF signaling pathway inhibitors have been associated with various toxicities including an increased risk of fatal adverse events [7,8]. Therefore, an identification of biomarkers for efficacy is necessary to select suitable patients for this therapeutic approach. Molecules related to the underlying biology of RCC have been investigated as potential biomarkers for prediction of therapeutic benefit. The

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development of biomarkers requires clinical validity, or the ability of the assay to predict the clinical endpoint of interest as well as clinical utility meaning that the biomarker is actionable for informing treatment decisions in a manner that provides improved patient outcome [9]. In 1996, the American Society of Clinical Oncology Tumor Markers Guidelines Committee recommended the five Levels of evidence (LOE) to determine the clinical validity and utility of a biomarker [10]. Simon et al. proposed an updated revision of the LOE scale providing more precise definitions of key elements for biomarker studies that constitute LOE determination [9]. There has been no systematic attempt to review and grade biomarkers for VEGF-targeted therapy using this standardized LOE scale. Therefore, we conducted a systematic review and graded the LOE in studies that assessed the clinical validity and utility of biomarkers for VEGF signaling pathway inhibitors in patients with metastatic RCC.

Methods

Study selection

Studies were selected and systemically reviewed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. Studies were considered eligible if biomarkers obtained from metastatic clear-cell RCC patients treated with the FDA-approved VEGF-targeted therapy were assessed for their correlation with clinical outcomes. Eligible clinical outcomes included a response rate based on the Response Evaluation Criteria in Solid Tumors (RECIST), progression-free survival (PFS), and overall survival (OS) [12]. We only considered genetic, proteomic and cellular biomarkers related to the pathways targeted by the VEGF-targeted agents or the alternative pathways that may mediate resistance and genomics which can modulate drug metabolism and mediate activity. Studies were excluded if they only assessed laboratory-based factors such as electrolytes, red blood cells, white blood cells, platelets, liver enzymes, lactate dehydrogenase, erythrocyte sedimentation rate and C-reactive protein. We included studies with a sample size greater than 10 patients because the ability to evaluate any biomarkers would be negligible in smaller studies.

Search strategy

We conducted a review of PubMed from January 1966 to August 2013. The search keywords were: <axitinib OR bevacizumab OR pazopanib OR sorafenib OR sunitinib>, <renal cell carcinoma>, and <biomarker* OR predict* OR prognos*>. We also searched abstracts and virtual meeting presentations containing the same search terms from the American Society of Clinical Oncology (ASCO) conferences held up to March 2013 in order to identify relevant studies. An independent search of the Web of Science, Embase and Cochrane electronic databases was also performed to ensure that no additional studies were overlooked. In cases of duplicate publications, only the most complete, recent, and updated report of the study was included. Independent reviewers (TF and CHL) screened reports that included the key terms by their titles and abstracts for relevance. Finally, full texts of the relevant articles were retrieved to assess eligibility.

Data extraction

Two investigators (TF and CHL) independently performed data extraction. Any discrepancies between reviewers were resolved by consensus. The following information was recorded for each study: first author's name, year of publication, source of patient data, treatment (line of treatment), sample size, material, methodology, biomarkers studied, clinical outcomes, statistical methods and cut-off point.

Outcome definition

Biomarkers can play roles in predictive and prognostic characterizations of a patient's disease. Predictive biomarkers indicate whether a patient will benefit from a given treatment. Prognostic biomarkers provide information about a patient's likely clinical outcomes with or without treatment. To establish a predictive biomarker, controlled studies are required, while a prognostic biomarker can be established with single arm studies. We examined the clinical validity and utility of biomarkers on the basis of the criteria originally proposed by Hayes et al. and revised by Simon et al. [9,10]. The key elements of biomarker studies that are used to generate a Levels of evidence (LOE) determination included characteristics of (1) clinical trial design; (2) patients and patient data; (3) specimen collection, processing, and archival; (4) statistical design and analysis; and (5) consistency in validation results. According to the scale, Category A study represents prospective randomized clinical trials designed and powered specifically to address biomarker questions. Category B study represents prospective studies not primarily designed to address biomarker questions, rather archive specimens for retrospective analysis of biomarkers. Category C study represents prospective, observational registry studies. Category D study represents retrospective, observational studies. Level I evidence is defined as at least one study from Category A, or one or more studies from Category B with consistent results. Level II evidence includes at least one study from Category B or two or more studies from Category C with consistent results. Level III evidence includes at least one study from Category C, and Levels IV and V evidence includes studies from Category D. Based on this scale, two investigators (TF and CHL) independently graded the studies. If there were any discrepancies between the reviewers, a third investigator (JJH) reviewed the article and finalized the grading.

Results

Search results

Our search strategy yielded 474 potentially relevant articles in PubMed. 371 articles were excluded during the initial title and abstract screening. The remaining 105 articles were retrieved for full review and 59 articles were excluded. We also included four studies from ASCO presentations. Supplement 1 outlines the selection process and reasons for study exclusion. Tran et al. [47] and Figueroa et al. [61] obtained samples from a phase II and a phase III trial and assessed the biomarkers in each trial independently. We considered their analysis of biomarkers using each trial as independent study. A total of 50 articles (52 studies) were selected for this review.

Evaluation of biomarker studies

We found no prospective controlled trial designed to address biomarkers (Category A study). There were 21 Category B studies which evaluated candidate biomarkers based on archived specimens from previously conducted clinical trials. Seven studies assessed the predictive value of biomarkers for VEGF-targeted therapy using the archived specimens from randomized trials [25,32,35,47,50,60,62]. The prognostic value of biomarkers for VEGF-targeted therapy was evaluated in 17 Category B studies. 20 studies satisfied Category C criteria. 14 studies were prospective