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Progression-free survival as primary endpoint in randomized clinical trials of targeted agents for advanced renal cell carcinoma. Correlation with overall survival, benchmarking and power analysis

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Abstract

Purpose: A correlation, power and benchmarking analysis between progression-free and overall survival (PFS, OS) of randomized trials with targeted agents or immunotherapy for advanced renal cell carcinoma (RCC) was performed to provide a practical tool for clinical trial design.

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Results: For 1st-line of treatment, a significant correlation was observed between 6-month PFS and 12-month OS, between 3-month PFS and 9-month OS and between the distributions of the cumulative PFS and OS estimates. According to the regression equation derived for 1st-line targeted agents, 7859, 2873, 712, and 190 patients would be required to determine a 3%, 5%, 10% and 20% PFS advantage at 6 months, corresponding to an absolute increase in 12-month OS rates of 2%, 3%, 6% and 11%, respectively.
Conclusions: These data support PFS as a reliable endpoint for advanced RCC receiving up-front therapies. Benchmarking and power analyses, on the basis of the updated survival expectations, may represent practical tools for future trial' design.

Keywords: Correlation; Overall survival; Progression-free survival; Renal cell carcinoma

1. Introduction

Since 2006, many active targeted agents have been approved for the treatment of advanced renal cell carcinoma (RCC), leading to an important improvement in RCC management, as compared with the past [1].

With the exception of temsirolimus [2], targeted agents have been registered on the basis of an advantage in progression free survival (PFS), without significant differences in overall survival (OS). The lack of OS benefit in individual studies may be, in part, explained by cross-over issues and by the availability of multiple subsequent lines of active therapy, which dilute out potential OS advantages [3].

Nevertheless, OS remains the gold standard for the evaluation of clinical efficacy of an experimental drug, because it is the only end-point able to directly demonstrate a relevant clinical benefit and is completely independent of investigator biases, including timing of disease assessment. Although objective, OS requires large patient populations and long follow-up, with higher study costs and longer duration, potentially delaying patients' access to new active treatments. Moreover, Broglio and Berry demonstrated that, in many clinical trials for metastatic diseases, a long median post-progression survival may confound OS comparisons [4]. In such cases, a lack of statistical significance in OS differences does not imply an actual lack of improvement, since OS endpoints may not accurately reflect the benefit of the agent under investigation.

Many studies have been conducted in solid tumors to assess whether PFS is indeed a reliable surrogate end-point, regardless of disease and setting [5–7], particularly in modern age, in which small benefits at high costs will no longer be affordable [8]. This concept especially applies to the development of new drugs with a mechanism of action similar to that of already approved agents, as I happens with agents targeting the VEGF/VEGFR axis or the mTOR pathway in metastatic RCC, a disease setting in which a plethora of active agents is already available across multiple lines of treatment.

In order to provide a practical tool for clinical trial design in such context, we performed a pooled correlation analysis between PFS and OS according to treatment strategy using a meta-analytic approach and a power and benchmarking analysis of randomized clinical trials conducted in the setting of advanced RCC.

2. Materials and methods

The analysis was conducted according to 4 pre-specified steps: (1) definition of the question the analysis was designed to answer; (2) definition of the trial selection criteria; (3) definition of the search strategy; and (4) detailed description of the statistical methods.

2.1. Outcome definition

The analysis was conducted to assess if a correlation between PFS and OS may be demonstrated in clinical trials evaluating specific treatments (targeted therapies, immunotherapy and placebo) for advanced RCC.

2.2. Data extraction and synthesis

Full reports and trials' updates were gathered through Medline (PubMed), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Association of Urology (EAU) and American Urological Association (AUA) website searches. Keywords used for searching were: renal cell carcinoma, RCC, immunotherapy, cytokines, phase 3, and randomized, tyrosine kinase inhibitors. Furthermore, meetings lectures having RCC as the topic were checked.

All phase 3 randomized trials published in peer-reviewed journals or presented at the ASCO, ASCO-Genitourinary Symposium, ECCO, and ESMO meetings up to December 31st 2013, accruing either treatment-naïve or pretreated advanced RCC patients to receive targeted agents, immunotherapy or placebo were considered eligible. Trials examining first-line targeted agent administration after only one previous systemic treatment consisting of cytokines (as in the TARGET [9], pazopanib registration [10], and AXIS [11] trials) were included among first-line trials. As a mandatory entry criterion, both PFS and OS data (as a direct report or extracted by curves) with at least a 12-month follow-up must have been reported. Given the purpose of the current analysis (correlation between efficacy outcomes), randomized phase II trials were excluded. Trial arms examining chemotherapy, radiotherapy, experimental combinations or drugs without Food and Drug Administration (FDA) and/or European Medical Agency (EMA) regulatory approval were