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Impact of targeted therapies in metastatic renal cell carcinoma on patient-reported outcomes: Methodology of clinical trials and clinical benefit

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ABSTRACT

Background: Molecular targeted therapies have improved progression-free survival (PFS) without translating systematically into overall survival (OS) for patients with metastatic renal cell carcinoma (mRCC). In this population, patient-reported outcomes (PROs) have become a significant outcome. We evaluated the methodological quality of the assessment of PROs in randomized controlled trials (RCTs) and the clinical benefit of the different treatments including survival and quality of life (QoL).
Methods: A systematic review identified RCTs published between January 2005 and July 2014. They were evaluated according to 11 items derived from the 2013 CONSORT PROs reporting guidelines. Survival outcomes and PROs main results were analyzed and the magnitude of clinical benefit was assessed with the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS).
Results: 12 RCTs were included with a total of 22 publications. The mean CONSORT score for all items was 4.5 on an 11-point scale. No publication reported the power of the PROs analysis and only one reported a PRO hypothesis. 50% of studies did not interpret PROs in relation to clinical outcomes and only 18% discussed specific limitations of PROs and their implications for generalizability. By adding the QoL criterion to PFS, 4 trials (36.4%) obtained a high level of proven clinical benefit according to the ESMO-MCBS.
Conclusion: The methodology for assessing PROs in mRCC is not optimal. Efforts should focus on defining PROs endpoint and increasing the quality of reporting of QoL.
Conclusion: New-generation therapies in mRCC should demonstrate a gain not only in survival but also in QoL to be included in the therapeutic arsenal.

Introduction

Metastatic renal cell carcinoma (mRCC) is one of the most treatment-resistant malignancies to conventional cytotoxic chemotherapy. Previously, systemic treatment was limited to cytokine therapy [1]. Treatment options have expanded considerably for patients with mRCC with the greater understanding of the molecular mechanisms involved [2–4]. Seven molecular targeted agents for the treatment of mRCC are now approved, with significant improvements in progression-free survival (PFS) but rarely with an impact on overall survival (OS) [5]. They are better tolerated than cytokine therapy but can cause side-effects with different toxicity profiles. They can also impact on quality of life (QoL), which is a discriminating factor when choosing treatment, especially in the long-term.

To evaluate the clinical benefit of new treatment, the European Society for Medical Oncology (ESMO) has developed a validated tool to assess the magnitude of clinical benefit based on improvements in survival and/or QoL [6].

Health-related quality of life (HRQoL) has become a significant outcome in this population and recent pivotal trials have included measurement of QoL with assessment of patient-reported outcomes (PROs) [7,8].

PROs measures provide a better evaluation of patients' symptoms, functioning and general well-being and may have an impact on clinical decision-making [9]. However, the methodology for assessing PROs and reporting their data are often not optimal whereas some guidelines are nowadays available [10].

This review evaluates the methodological quality of PROs reporting according to the 2013 CONSORT PROs reporting guidelines [11] in randomized controlled trials (RCTs) evaluating molecular targeted therapies in mRCC. In addition, we analyzed the

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clinical benefit of these main molecules according to the ESMO-MCBS.

Materials and methods

Study selection

An electronic literature search was conducted in Medline via Pubmed from January 2005 to July 2015. The search was carried out using the keywords terms "cancer", "randomized", "phase III", "renal" and "metastatic". The terms were combined with "target therapy", "quality of life" and "patient-reported outcomes" using the Boolean operator "and". Only English language RCTs with at least one PRO as primary or secondary endpoint evaluating molecular targeted therapies in patients with mRCC were considered. Abstracts and case reports were excluded. Moreover, additional pertinent publications were added by reviewing reference lists of studies of interest. Secondary reports of PROs of the same trial were also analyzed.

Data extraction

All identified RCTs and extracted data were analyzed by two independent reviewers: study characteristics, number of patients, study drug, line of therapy, primary and secondary endpoints, PROs scales used, summary of efficacy, safety and PROs assessments.

In case of discrepancies, all reviewers revised the paper to reconcile any differences. Unresolved differences were at last discussed with the senior author (F.J).

Quality assessment of PROs reporting

Methodological quality was assessed using a standardized PROs reporting quality score based on items derived from the 2013 PROs extension of the CONSORT guidelines [11].

The final CONSORT PRO guidance identifies 5-items extension relating to PROs.

The items specific to PROs are (1) that the PROs be identified as a primary or secondary outcome in the abstract; (2) that a description of the hypothesis and relevant domains be provided; (3) that evidence of instrument validity and reliability be provided or cited; (4) that the statistical approaches for dealing with missing data be explicitly stated; and (5) that PRO–specific limitations of study findings and generalizability of results to other populations and clinical practice be discussed.

Although an extension was deemed unnecessary for a number of existing CONSORT checklist items, we decided to add the 6 additional PRO-specific elaborations as recommended by the CONSORT guidelines and already used in previous study [12]. We finally got a score scale based on 11 items (5 extension and 6 elaboration statements) for a complete analysis.

Each item was scored 1 if it was adequately reported or 0 if it was not clearly reported or not reported at all: the higher the score, the higher the quality.

Magnitude of clinical benefit

Clinical benefit was evaluated with the ESMO-MCBS [6]. The ESMO-MCBS can be applied to comparative outcome studies evaluating the relative benefit of treatments using outcomes of survival, QoL, surrogate outcomes for survival or QoL or treatment toxicity in solid cancers.

This tool makes it possible to assign the highest grade (4–5) to trials having adequate power for a relevant magnitude of benefit and to make appropriate grade adjustment by taking into account toxicity and QoL.

In order to calculate the grade, the variability of the estimated hazard ratio (HR) from a study, the lower limit of the 95% confidence interval (CI) for the HR is compared with specified threshold values; and secondly the observed absolute difference in treatment outcomes is compared with the minimum absolute gain considered as beneficial are necessary.

The tool is presented in two parts. Form 1 is used to evaluate adjuvant and other treatments with curative intent. Form 2 (a, b or c) is used to evaluate noncurative interventions, with form 2a for studies with OS as the primary outcome, form 2b for studies with PFS as primary outcomes, 2c for studies with QoL, toxicity or response rate as primary outcomes and for non-inferiority studies.

In our case, we used only form 2 of the scale reserved for noncurative interventions. For forms 2a and 2b, it is possible to upgrade by one level if QoL is improved or if less than grade 3–4 toxicities that bother patients are demonstrated. Alternatively, one can downgrade by one level if there is one or more of the above incremental toxicities associated with the new drug or if the drug only leads to improved PFS but not QoL.

Results

Identified studies

The systematic search identified 216 published articles. After excluding those that did not meet the inclusion criteria, we selected 22 publications included 12 RCTs (10 were secondary reports of PROs identified in 5 studies). Details on the selection process were documented with the Prisma Flow Diagram (Fig. 1).

Quality assessment of PROs reporting based on the 2013 CONSORT PROs guidelines (Table 1)

The mean score for all items was 4.5 on an 11-point scale (range: 0–11), only 1 publication had a maximum score corresponding to a secondary report [13]. Based only on the 5-items extension, the mean score was 1.8 on 5-point scale (range: 0–5) with a maximum of 5 points for 2 publications [13,20]. The most frequently reported items for PRO-specific extension and elaboration were respectively: the evidence of instrument validity of PROs (55%) and the number of participants included in each analysis required for PROs results (55%). PROs as a primary or secondary outcome in the abstract and/or rationale for the assessment of PROs were described in 41% of publications. However, no publication reported the power of the PROs analysis and only one proposed the impact of the benefits.

Most articles (82%) correctly reported the reference of the PROs instrument but no data on the collection methods were reported and only 1/3 described a statistical approach for dealing with missing data.

The assessment of PROs at each time-point was documented in 50% of the cases and a summary of the results was provided only in 32%. Results from each domain for multidimensional PROs were cited in 41%. In the discussion, half of the publications offered an interpretation of PRO data in relation to clinical outcomes but only 4 (18%) discussed the specific limitations of PROs and the implications for generalizability.

Summary of main results with their magnitude of clinical benefit (Table 2)

Median survival gain with their estimated HR, QoL and treatment toxicity were extracted in order to evaluate the relative