



Cochrane
Library

Cochrane Database of Systematic Reviews

Immunotherapy for metastatic renal cell carcinoma (Review)

Unverzagt S, Moldenhauer I, Nothacker M, Roßmeißl D, Hadjinicolaou AV, Peinemann F, Greco F, Seliger B

Unverzagt S, Moldenhauer I, Nothacker M, Roßmeißl D, Hadjinicolaou AV, Peinemann F, Greco F, Seliger B.

Immunotherapy for metastatic renal cell carcinoma.

Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD011673.

DOI: [10.1002/14651858.CD011673.pub2](https://doi.org/10.1002/14651858.CD011673.pub2).

www.cochranelibrary.com

Immunotherapy for metastatic renal cell carcinoma (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

[Intervention Review]

Immunotherapy for metastatic renal cell carcinoma

Susanne Unverzagt¹, Ines Moldenhauer², Monika Nothacker³, Dorothea Roßmeißl⁴, Andreas V Hadjinicolaou⁵, Frank Peinemann⁶, Francesco Greco⁷, Barbara Seliger⁸

¹Institute of Medical Epidemiology, Biostatistics and Informatics, Martin Luther University Halle-Wittenberg, Halle/Saale, Germany. ²Martin Luther University Halle-Wittenberg, Halle/Saale, Germany. ³AWMF Institute for Medical Knowledge Management, Marburg, Germany. ⁴Medical Faculty, Martin Luther University Halle-Wittenberg, Halle/Saale, Germany. ⁵Human Immunology Unit, Institute of Molecular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, UK. ⁶Pediatric Oncology and Hematology, Children's Hospital, University of Cologne, Cologne, Germany. ⁷Department of Urology and Renal Transplantation, Martin Luther University Halle-Wittenberg, Halle/Saale, Germany. ⁸Institute of Medical Immunology, Martin Luther University Halle-Wittenberg, Halle/Saale, Germany

Contact: Susanne Unverzagt, Institute of Medical Epidemiology, Biostatistics and Informatics, Martin Luther University Halle-Wittenberg, Magdeburger Straße 8, Halle/Saale, 06097, Germany. susanne.unverzagt@medizin.uni-halle.de.

Editorial group: Cochrane Urology Group.

Publication status and date: New, published in Issue 5, 2017.

Citation: Unverzagt S, Moldenhauer I, Nothacker M, Roßmeißl D, Hadjinicolaou AV, Peinemann F, Greco F, Seliger B. Immunotherapy for metastatic renal cell carcinoma. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD011673. DOI: [10.1002/14651858.CD011673.pub2](https://doi.org/10.1002/14651858.CD011673.pub2).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Since the mid-2000s, the field of metastatic renal cell carcinoma (mRCC) has experienced a paradigm shift from non-specific therapy with broad-acting cytokines to specific regimens, which directly target the cancer, the tumour microenvironment, or both.

Current guidelines recommend targeted therapies with agents such as sunitinib, pazopanib or temsirolimus (for people with poor prognosis) as the standard of care for first-line treatment of people with mRCC and mention non-specific cytokines as an alternative option for selected patients.

In November 2015, nivolumab, a checkpoint inhibitor directed against programmed death-1 (PD-1), was approved as the first specific immunotherapeutic agent as second-line therapy in previously treated mRCC patients.

Objectives

To assess the effects of immunotherapies either alone or in combination with standard targeted therapies for the treatment of metastatic renal cell carcinoma and their efficacy to maximize patient benefit.

Search methods

We searched the Cochrane Library, MEDLINE (Ovid), Embase (Ovid), ISI Web of Science and registers of ongoing clinical trials in November 2016 without language restrictions. We scanned reference lists and contacted experts in the field to obtain further information.

Selection criteria

We included randomized controlled trials (RCTs) and quasi-RCTs with or without blinding involving people with mRCC.

Data collection and analysis

We collected and analyzed studies according to the published protocol. Summary statistics for the primary endpoints were risk ratios (RRs) and mean differences (MD) with their 95% confidence intervals (CIs). We rated the quality of evidence using GRADE methodology and summarized the quality and magnitude of relative and absolute effects for each primary outcome in our 'Summary of findings' tables.

Immunotherapy for metastatic renal cell carcinoma (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Main results

We identified eight studies with 4732 eligible participants and an additional 13 ongoing studies. We categorized studies into comparisons, all against standard therapy accordingly as first-line (five comparisons) or second-line therapy (one comparison) for mRCC.

Interferon (IFN)- α monotherapy probably increases one-year overall mortality compared to standard targeted therapies with temsirolimus or sunitinib (RR 1.30, 95% CI 1.13 to 1.51; 2 studies; 1166 participants; moderate-quality evidence), may lead to similar quality of life (QoL) (e.g. MD -5.58 points, 95% CI -7.25 to -3.91 for Functional Assessment of Cancer - General (FACT-G); 1 study; 730 participants; low-quality evidence) and may slightly increase the incidence of adverse events (AEs) grade 3 or greater (RR 1.17, 95% CI 1.03 to 1.32; 1 study; 408 participants; low-quality evidence).

There is probably no difference between IFN- α plus temsirolimus and temsirolimus alone for one-year overall mortality (RR 1.13, 95% CI 0.95 to 1.34; 1 study; 419 participants; moderate-quality evidence), but the incidence of AEs of 3 or greater may be increased (RR 1.30, 95% CI 1.17 to 1.45; 1 study; 416 participants; low-quality evidence). There was no information on QoL.

IFN- α alone may slightly increase one-year overall mortality compared to IFN- α plus bevacizumab (RR 1.17, 95% CI 1.00 to 1.36; 2 studies; 1381 participants; low-quality evidence). This effect is probably accompanied by a lower incidence of AEs of grade 3 or greater (RR 0.77, 95% CI 0.71 to 0.84; 2 studies; 1350 participants; moderate-quality evidence). QoL could not be evaluated due to insufficient data.

Treatment with IFN- α plus bevacizumab or standard targeted therapy (sunitinib) may lead to similar one-year overall mortality (RR 0.37, 95% CI 0.13 to 1.08; 1 study; 83 participants; low-quality evidence) and AEs of grade 3 or greater (RR 1.18, 95% CI 0.85 to 1.62; 1 study; 82 participants; low-quality evidence). QoL could not be evaluated due to insufficient data.

Treatment with vaccines (e.g. MVA-5T4 or IMA901) or standard therapy may lead to similar one-year overall mortality (RR 1.10, 95% CI 0.91 to 1.32; low-quality evidence) and AEs of grade 3 or greater (RR 1.16, 95% CI 0.97 to 1.39; 2 studies; 1065 participants; low-quality evidence). QoL could not be evaluated due to insufficient data.

In previously treated patients, targeted immunotherapy (nivolumab) probably reduces one-year overall mortality compared to standard targeted therapy with everolimus (RR 0.70, 95% CI 0.56 to 0.87; 1 study; 821 participants; moderate-quality evidence), probably improves QoL (e.g. RR 1.51, 95% CI 1.28 to 1.78 for clinically relevant improvement of the FACT-Kidney Symptom Index Disease Related Symptoms (FKSI-DRS); 1 study, 704 participants; moderate-quality evidence) and probably reduces the incidence of AEs grade 3 or greater (RR 0.51, 95% CI 0.40 to 0.65; 1 study; 803 participants; moderate-quality evidence).

Authors' conclusions

Evidence of moderate quality demonstrates that IFN- α monotherapy increases mortality compared to standard targeted therapies alone, whereas there is no difference if IFN is combined with standard targeted therapies. Evidence of low quality demonstrates that QoL is worse with IFN alone and that severe AEs are increased with IFN alone or in combination. There is low-quality evidence that IFN- α alone increases mortality but moderate-quality evidence on decreased AEs compared to IFN- α plus bevacizumab. Low-quality evidence shows no difference for IFN- α plus bevacizumab compared to sunitinib with respect to mortality and severe AEs. Low-quality evidence demonstrates no difference of vaccine treatment compared to standard targeted therapies in mortality and AEs, whereas there is moderate-quality evidence that targeted immunotherapies reduce mortality and AEs and improve QoL.

PLAIN LANGUAGE SUMMARY

Immunotherapy for advanced kidney cancer

Review question

Kidney cancer is rarely curable once it has spread to other organs at the time of diagnosis. Targeted agents are currently considered as the standard treatment for advanced kidney cancer that has spread to other organs. This review examines clinical studies that have directly compared immunotherapies or combination therapies to current standard therapy.

Background

Prior to the use of the new targeted agents, drugs that boosted the immune response against the cancer in a non-specific way (immunotherapies) were the most widely used treatment form for people with kidney cancer that had spread to other organs. Newer immunotherapeutic agents, including vaccines and so called 'checkpoint inhibitors,' have been developed to specifically target the body's immune system and enable it to recognize and attack cancer cells more specifically. In this review, we evaluated all types of immunotherapy or combination therapies by comparing it to the current standard therapy.

Study characteristics

A systematic search up to the end of October 2016 identified eight studies that looked at four different types of immunotherapy in 4732 people. Studies were only included if patients were randomized to a form of immunotherapy included in this review or a standard form of targeted therapy. One study was funded by a public institution whereas all the others were supported by drug companies.

Immunotherapy for metastatic renal cell carcinoma (Review)

The study participants were generally representative of people with advanced kidney cancer. The majority of people had their kidney cancer removed before starting treatment. We compared studies of people who had previously received standard medicine (821 participants) to those of people who had not (3911 participants). All studies reported our main outcome of interest; the chance of longer survival including the survival for one year. We also focused on the frequency of severe treatment side effects, quality of life and the delay in disease worsening.

Key results

Interferon- α was the most commonly used therapy option prior to the era of targeted therapies. Two studies with 1166 participants compared interferon- α alone (monotherapy) to targeted standard therapy. Interferon- α is probably inferior to tested targeted therapies called sunitinib and temsirolimus. Patients with interferon- α monotherapy probably have a shorter time to worsening of cancer. They may have similar quality of life and a slightly more severe treatment side effects.

Adding temsirolimus to interferon- α probably does not improve survival compared to temsirolimus alone, but may result in more major side effects (one study).

Two studies compared interferon- α to a combination of interferon- α and bevacizumab in 1381 previously untreated participants. There was a slightly increased death rate with probably fewer major side effects for people treated with interferon- α alone.

Two studies evaluated vaccines. Vaccines may lead to similar death rates and side effects in people with advanced kidney cancer.

For patients who had already undergone systemic treatment, one study with nivolumab, a novel checkpoint inhibitor, improved average survival by more than five months when compared to the targeted standard therapy, everolimus. The effects are probably accompanied by better quality of life and fewer major side effects.

Quality of the evidence

We had reduced confidence in the results of the studies we analyzed (moderate- or low-quality evidence) because patients and treating physicians were often not blinded to the treatment and involved relatively few patients.