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Chemoimmunotherapy in Advanced Renal Cell Carcinoma: A Case Report of a Long-Term Survivor Adjunctly Treated with *Viscum album* Extracts

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Keywords
Renal clear cell carcinoma · Interleukin-2 · Interferon-α2a · 13-*cis*-Retinoic acid · *Viscum album*

Abstract
Introduction: Metastatic renal cell carcinoma has a poor prognosis. Treatment approaches with immunotherapy show promising results in subpopulations. *Viscum album* extracts – used as an adjunct to cancer treatment – have cytotoxic, apoptogenic, and immune-stimulating properties and show synergistic effects with chemotherapy agents. ***Case Report:*** A 51-year-old man was diagnosed with metastatic renal cell carcinoma of clear cell histology which was classified as pT3a, N1, M1, G3. Nephrectomy was performed, and the patient received chemoimmunotherapy (interferon-α2a, interleukin-2, fluorouracil, isotretinoin). Additionally, he received *V. album* extracts as intravenous infusions and subcutaneous injections. One year after surgery, the patient was in complete remission, which is ongoing 18 years after the initial diagnosis. ***Discussion:*** This case shows an extraordinarily long survival of a metastasized renal cell carcinoma patient under chemoimmunotherapy and fever-inducing *V. album* extracts. This combined treatment might have synergistically contributed to tumor remission and control. With regard to clinical relevance, further investigations are needed.

Schlüsselwörter
Klarzelliges Nierenzellkarzinom · Interleukin-2 · Interferon-α2a · 13-*cis*-Retinsäure · *Viscum album*

Zusammenfassung
Hintergrund: Das metastasierte klarzellige Nierenzellkarzinom hat eine schlechte Prognose. Behandlungsansätze mit Immuntherapien zeigen positive Ergebnisse in Subpopulationen. *Viscum-album*-Extrakte – als Begleitbehandlung in der Krebstherapie – haben zytotoxische, apoptosefördernde und immunstimulierende Eigenschaften und zeigen synergistische Effekte mit Chemotherapeutika. ***Fallbericht:*** Bei einem 51-jährigen Mann wurde ein metastasiertes klarzelliges Nierenzellkarzinom diagnostiziert, das als pT3a, N1, M1, G3 klassifiziert wurde. Es wurde eine Nephrektomie durchgeführt, und der Patient erhielt eine Immunochemotherapie (Interferon-α2a, Interleukin-2, Fluorouracil, Isotretinoin). Begleitend erhielt er intravenöse Infusionen und subkutane Injektionen mit *V.-album*-Extrakten. Ein Jahr nach der Operation war der Patient in einer vollständigen Remission, die nun bereits 18 Jahre seit der Erstdiagnose anhält. ***Diskussion:*** Dieser Fallbericht zeigt ein besonders langes Überleben eines Patienten mit metastasiertem Nierenzellkarzinom unter Immunochemotherapie und fieberin-

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duzierenden *V.-album*-Extrakten. Diese kombinierte Behandlung hat möglicherweise synergistisch zur Tumorremission und Tumorkontrolle beigetragen. Hinsichtlich der klinischen Relevanz sollten weitere Untersuchungen erfolgen.

Introduction

Cancer of the kidney has a high and rising incidence (12.1/100,000 in Europe [1]) with a male predominance of approximately 2:1. Risk factors are smoking, obesity, and hypertension [2]. Survival rates of kidney cancer have improved – especially due to early detection, refined surgical techniques, and new therapeutic agents [3].

Renal cell carcinoma (RCC) accounts for 90% of all kidney cancers, and clear cell carcinoma (ccRCC) is its most common histological subtype (approx. 75%). Recommended treatment is surgical excision/cytoreduction in all stages. Immunotherapy and targeted therapies are used in advanced stages of the disease [4]. Histologically, ccRCC shows extraordinarily high infiltration rates with T cells [5]; ccRCC shows a very high number of insertion-and-deletion mutations, when compared to other cancer types [6], and spontaneous remission of lung metastases has been occasionally reported [7, 8]. These properties make this tumor highly immunogenic.

Different species of *Viscum album* have been used in traditional medicines and have been widely investigated scientifically in the last few decades [9]. *V. album* extracts (VAE) – aqueous extracts from European mistletoe (*Viscum album* L.) – show a variety of antineoplastic properties: cytotoxic and proapoptotic effects, immune stimulation, downregulation of cancer genes (e.g., transforming growth factor β and matrix metalloproteinases), reduction of cell migration, and interference with tumor angiogenesis [9–12]. Pharmacologically active compounds include mistletoe lectins, viscotoxins, oligo- and polysaccharides, flavonoids, and triterpene acids [9]. Different commercial VAE preparations for injection (usually subcutaneously but also intralesionally or intravenously) are used as a supportive therapy in patients with cancer [13]. VAE are safe, even when used in higher dosages; they have dose-dependent, self-limited side effects such as erythema at the injection site, fever, flu-like symptoms, and rare pseudoallergic reactions [14, 15]. In a trial by Brinkman and Hertle [16], treatment with VAE was compared with immunotherapy in advanced RCC and showed fewer responses to therapy and fewer side effects. Tumor remission has been repeatedly described, usually under high-dose VAE treatment [17], and prolonged survival was seen in a trial of advanced pancreatic cancer patients [18].

Case Report

A 51-year-old wholesaler presented with chronic cough that he had experienced for 5 months. He had no additional symptoms, no hypertension, and a normal body weight; he had stopped smoking 12 years previously. He was diagnosed with metastatic RCC, and nephrectomy with metastasectomy (of the epicardial metastasis) was performed; due to low hemoglobin, after surgery 2 red cell concentrates had to be given. The primary tumor had a size of 110 × 90 × 95 mm. Histological investigations showed mainly clear cell carcinoma cells; however, spindle cell and granular cell regions were present. Radiological investigation showed pulmonary metastases, and the tumor was classified as pT3a, N1, M1, G3.

The patient was enrolled in a clinical trial investigating the efficacy and safety of chemoimmunotherapy, and he received 3 cycles of subcutaneous interferon-α2a (IF-α2a), interleukin-2 (IL-2), intravenous fluorouracil (5-FU) and oral isotretinoin [19]. The regimen was IF-α2a (5×10^6 IU/m^2, day 1, weeks 1 + 4; days 1, 3, 5, weeks 2–3; 10×10^6 IU/m^2, days 1, 3, 5, weeks 5–8), IL-2 (10×10^6 IU m^2, twice daily, days 3–5, weeks 1 + 4; 5×10^6 IU/m^2, days 1, 3, 5, weeks 2 + 3), and isotretinoin (20 mg thrice daily) over 8 weeks. He experienced nausea, vomiting, and weight loss of 12 kg during the treatment period.

The patient asked his general practitioner, who had special training in integrative medicine, for additional treatment and received VAE as intravenous infusions and subcutaneous injections in addition to the chemoimmunotherapy. This treatment was chosen to increase the quality of life and to contribute to tumor control. VAE infusions were administered bi-weekly, and subcutaneous VAE were injected twice weekly but not on days of chemoimmunotherapeutic treatment. After intravenous VAE treatment, the patient experienced a fever slightly above 38 °C, which resolved after 1.5 days. The subcutaneous injection sites showed signs of slight induration and inflammation, which were self-limited.

After 7 months of therapy, a partial response of the lung metastases was seen in computed tomography scan; 1 year after surgery, the patient was in complete remission of all tumor lesions, which remained stable until the publication of this report – 18 years after initial diagnosis – under continued subcutaneous VAE treatment (Fig. 1). The patient is currently enjoying good quality of life, has a body weight of 145 kg (size 176 cm), and takes amlodipine and losartan for hypertension.

Discussion

We report a case of extraordinarily long cancer-free survival of a patient with ccRCC stage IV. He underwent nephrectomy, metastasectomy (epicardial), chemoimmunotherapy, and VAE therapy. Under this treatment, the patient showed complete resolution of his lung metastases within 1 year, and he has remained disease-free for 17 years (18 years from initial diagnosis).

Long-time survival (>5 and >10 years) of metastatic RCC patients who showed complete remission under treatment combinations including high-dose IL-2 have previously been described [20–23], but late relapses after more than 10 years have also been reported [20]. The rationale for using IL-2-based immunotherapies in immunogenic cancer is the induction of proliferation of T-cell clones against the tumor tissue [24]. Relapse after therapy

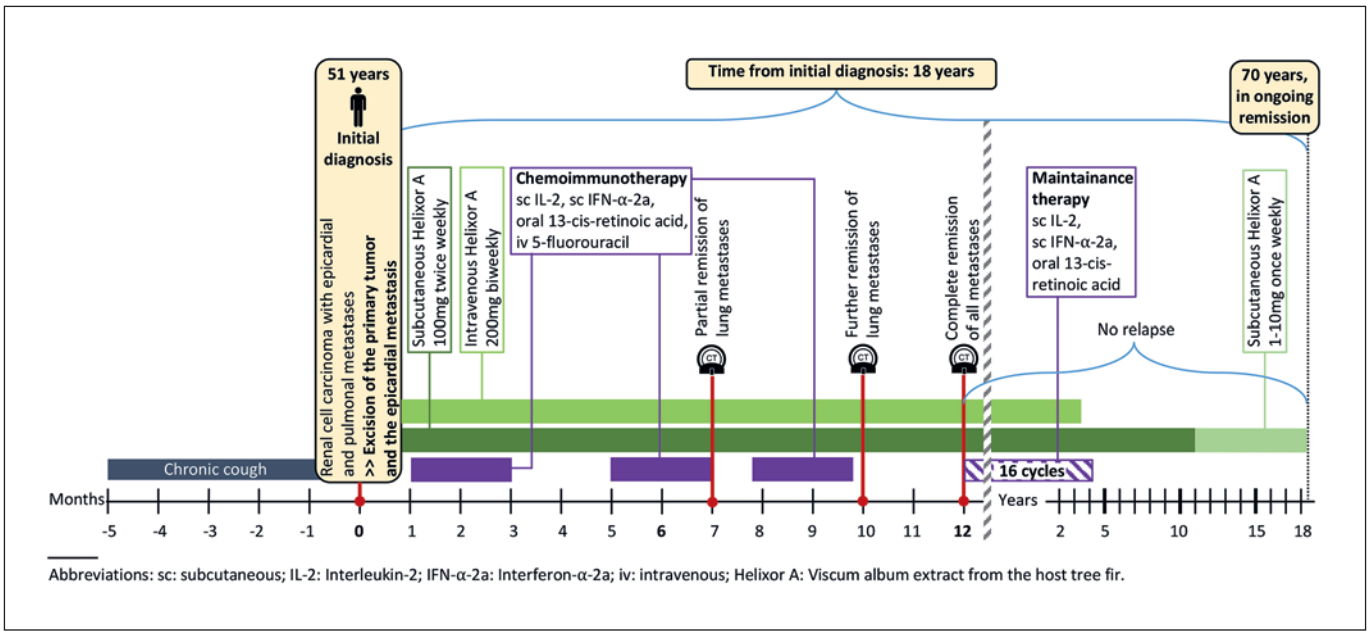

Fig. 1. Timeline of the patient with metastatic renal clear cell carcinoma.

can be interpreted as depletion of the respective T-cell clones.

VAE acts as an immune stimulant of pathways of the innate and adaptive immune system [9]. Subpopulations of T cells show proliferation after application of VAE. Hence, VAE may have contributed to a stronger proliferation induction of T-cell clones against the tumor tissue in the case presented here. Long-time treatment with VAE may have contributed to tumor control in stimulating further proliferation of the respective T-cell clones [9].

As this is the first report of a patient treated with a combination of IL-2-based immune therapy with VAE, it is important to note that the combination was well tolerated and did not lead to any severe side effects or immune system deterioration. However, our findings represent a singular case, and such a treatment cannot be recommended as standard treatment before more data are available. Similar observations of treatment safety are reported for combination therapy with immune checkpoint inhibitors with VAE [25].

The individual impact of the single agents used in this case cannot be conclusively determined; furthermore, even spontaneous remission of lung metastases after nephrectomy with long cancer-free survivals has been reported [7]. However, given the clinically relevant positive outcome of this case, further investigation should follow. The combined treatment of patients with VAE and IL-2-based immunotherapies as well as the use of VAE in RCC should be carefully documented and published to determine the directions of future research.

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Statement of Ethics

Informed consent was received from the patient for the publication of the report and accompanying images. The patient read the submission version of the report and confirmed its content.

Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

P.G.W., L.K., and G.S.K. contributed to the case report design. L.K. was the physician in charge who provided the patient's information. P.G.W. and L.K. collected and provided the data. P.G.W. was the principal author of the paper, had full access to all data, and is the guarantor. G.S.K. supervised the report and the publication process.

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