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The Future Therapy of Renal Cell Carcinoma? Non-Invasive Physical Plasma as an Innovative Oncological Therapy Modality

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Abstract

Renal cell carcinoma (RCC) is one of the most important urological tumors and is one of the most common cancer diseases worldwide. Unfortunately, the treatment options are very limited due to resistances. Non-invasive physical plasma (NIPP) is currently becoming a promising and very well tolerated treatment option for cancer. NIPP represents a highly energized gas and induces varying antioncogenic cell responses in tumor cells. And also in the case of RCC, NIPP treatment has great potential to enhance and supplement existing anticancer treatment options. Outstanding characteristics of NIPP treatment are 1) a precise and local effect on the treated tissue and 2) an almost exclusive effect on treated tumor cells without side effects. This allows an enormously large therapeutic window and makes the combination of NIPP treatment and classical therapy appear particularly promising. In addition to RCC, plasma oncology offers an extremely innovative physical treatment method for future oncology in general. This brief review article summarizes the current knowledge on the potential use of NIPP in RCC therapy.

Keywords

Physical Plasma, Non-Invasive Physical Plasma, Cold Plasma, Plasma Medicine, Plasma Oncology, Renal Cell Carcinoma

1. Introduction

With an incidence of 17.4 new cases per 100,000 inhabitants in 2018, renal cell carcinoma (RCC) is one of the ten most common malignant diseases in Germany [1]. Among urological carcinomas, RCC is the third most common after pros-

tate and bladder carcinomas. Men (25.1/100,000 inhabitants) are affected about twice as often as women (11.4/100,000 inhabitants) [1]. RCC accounts for 85% of kidney tumors [1] [2]. The mean age of onset is 68 years for men and 71 years for women [2] [3].

Tobacco consumption is considered a significant risk factor for RCC [4]. The risk increase is estimated to be 54% for men and 22% for women [5] [6] [7]. Overweight and high blood pressure also increases the risk of RCC [8] [9] [10]. Risk factors that cannot be influenced include terminal kidney failure [11] and familial high incidence of RCC [12]. The risk of developing RCC is 200% - 400% higher in first- or second-degree relatives of an existing patient [12] [13]. Germline mutations of a hereditary tumor are responsible for 1% - 4% of RCC [4]. These include von Hippel-Lindau syndrome, Birt-Hogg-Dubé syndrome, and hereditary leiomyomatosis [4].

RCC can be classified histologically. The most common entities are clear cell RCC (70% - 80%) and papillary RCC (15%). Other entities account for only about 1 % each [14] [15]. Staging is based on TNM and UICC criteria.

The prognosis of RCC is not excessively bad. The relative 5-year survival rate is over 75% [2]. However, the 5-year survival rate is strongly dependent on the tumor stage at initial diagnosis and decreases from more than 94% in stage I UICC (tumor up to 7 cm, no lymph node or distant metastases) to less than 17% in stage IV (tumor infiltrates beyond the gerota fascia or distant metastases are present) [2] [16]. 15% - 18% of all RCC are already in stage IV at initial diagnosis [16].

2. Current Renal Cell Carcinoma Therapies

Previous therapy concepts have been dependent on the tumor stage and the general condition of the patient. Patients with extensive comorbidities and/or a limited life expectancy with small kidney tumors can be actively monitored [4] [17]. In these patients, focal therapy such as cryo- or radiofrequency ablation can also be applied [4] [18] [19] [20].

Surgical resection of the tumor is the focus of curative therapy [21]. For small localized tumors, kidney preserving surgery and partial nephrectomy should be performed [4] [19] [21] [22]. The standard procedure is open partial kidney resection according to the guidelines [4] [23] [24]. If a kidney preserving resection is not possible, a radical nephrectomy is performed [21]. In the treatment of patients with already metastasized RCC, palliative concepts are in the foreground [4]. In order to reduce the tumor burden, these patients will also be nephrectomized to reduce the tumor load, and if conditions are favorable (few, easily resectable metastases), a curative therapy concept can be pursued in patients in good general condition [4] [21] [25] [26].

Additionally to local surgical procedures a systemic therapy is applied. However, RCC show a high resistance to classical chemotherapeutic drugs [27]. The response rate of RCC to 5-fluorouracil or floxuridine therapy is only 5% - 8%

[28]. Immunotherapies with interferon-α or interleukin-2 show only slightly better response rates of 10% and 13% - 21%, respectively [29] [30]. Palliative chemotherapy or cytokine therapy should therefore not be performed in metastasized clear cell NCC [4] [31]. Chemoimmunotherapy should also be avoided according to the guideline [4]. The targeted drugs available today, such as tyrosine kinase and mTOR inhibitors, show a better response and have replaced classic chemotherapy and pure immunotherapy [4].

Sunitinib is recommended as a first-line treatment in patients with metastatic NCC and good or moderate prognosis [4] [31] [32] [33]. About 31% of patients respond to this therapy [31]. Treatment with sunitinib can extend median progression-free survival from 5 to 11 months [31]. Overall survival is also extended from 21.8 to 26.4 months [34]. Complete remission is rarely observed with sunitinib therapy [35]. Radiation therapy may be considered in palliative therapy concepts in the presence of brain/bone metastases, spinal compression and other symptomatic metastases, if the patient is in good general state of health [4] [36] [37] [38] [39].

3. Non-Invasive Physical Plasma Treatment as Oncological Therapy

Despite some therapeutic options, it still seems necessary to develop and evaluate further alternative procedures for RCC treatment. The efficacy of classical therapies is primarily limited by frequently occurring resistances. Treatment with non-invasive physical plasma (NIPP) offers an alternative. NIPP is a partially or completely ionized gas consisting of protons, neutrons, ions, free electrons, radicals, and electromagnetic radiation [40]. These components are in continuous interaction with each other and with the ambient atmosphere [40]. NIPP is formed by excitation of atoms and molecules of a gas when energy is supplied [40] [41]. Naturally occurring physical plasmas, such as stars, northern lights or thunderbolts, are hot plasmas with temperatures up to several million degrees Celsius [42]. NIPP have temperatures up to 45˚C [43].

The application of artificially generated physical plasmas is widespread. While hot plasmas are used for welding or cutting metallic materials, NIPP can be used for sterilization of heat-sensitive materials, for example in food industry [44] [45] [46]. The antibacterial effect of NIPP is utilized in the treatment of wounds [47]. In addition, NIPP appears to promote wound healing by moderately activating acute inflammatory reactions and primary wound healing cascades [48]. This makes NIPP particularly suitable for the treatment of chronic and infected wounds [49] [50].

The application of NIPP in oncological therapy is a new promising indication [51] [52]. Various studies have shown an antiproliferative effect of NIPP on different cancer cells [53]. For example, an effect on skin tumors [54], breast [55], ovarian [56], and lung cancer cells [57] has been demonstrated. An interesting option seems to be the combination of NIPP with cytostatic drugs. NIPP treat-

ment could improve the response of chemotherapy to cytostatic-resistant colorectal cancer cells [58].

The mechanisms of action of NIPP are not yet fully understood and are the subject of current studies. The causes of the antibacterial effect are discussed as damage to DNA by UV radiation, changes in membrane potential, impairment of membrane integrity, and the formation of reactive species [59] [60]. The antiproliferative effect of NIPP is due to the induction of apoptosis as well as the impairment of cell metabolism and membrane integrity (**Figure 1**) [61] [62].

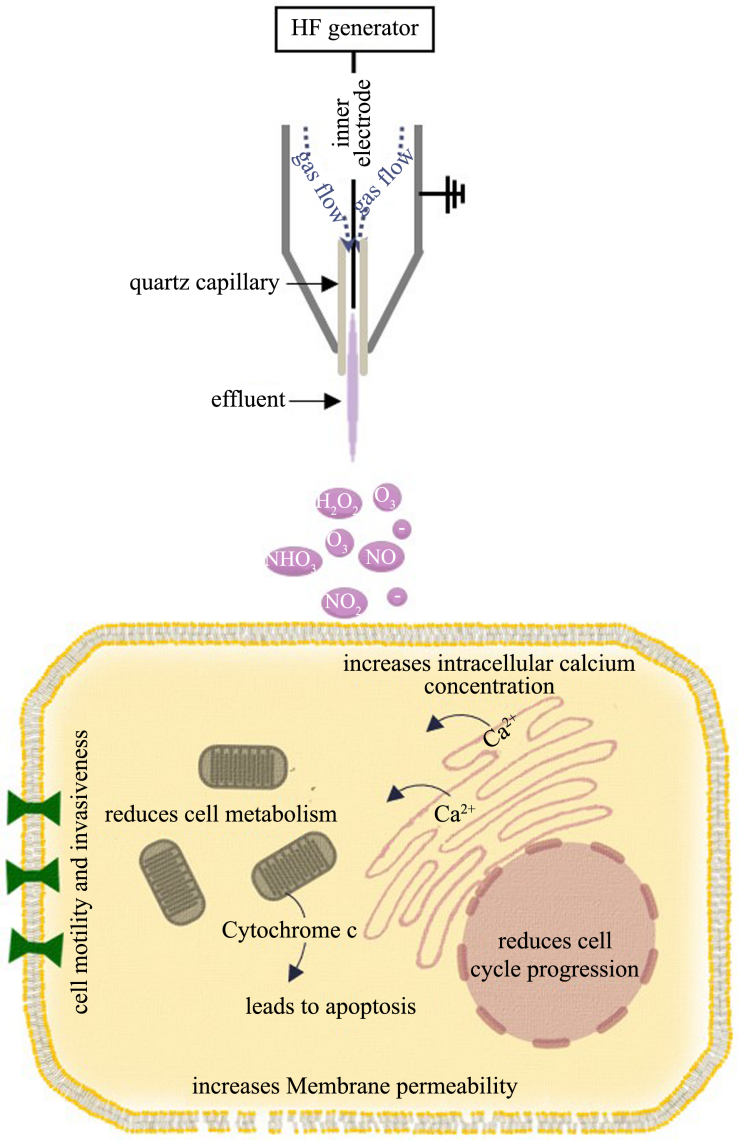

Figure 1. Antioncogenic activity of non-invasive physical plasma (NIPP). Reactive oxygen and nitrogen species are formed at the interface between NIPP and ambient atmosphere. These exert very different biological and primarily tumor suppressing effects on cancer cells. In renal cell carcinoma cells, treatment with NIPP leads to the release of intracellular Ca^{2+}. Furthermore, cell motility and membrane functionality are impaired, the metabolism is lowered and the cell cycle machinery is restricted. Subsequently, apoptotic signaling pathways are induced and programmed cell death occurs.

In addition to curative treatment approaches, NIPP could represent an extension of the treatment of palliative RCC patients. Compared to radiotherapy, NIPP offers several advantages. NIPP treatment does not induce necrosis and does severe or systemic inflammation [63]. Furthermore, the penetration depth of NIPP is comparatively low, so that tumor areas can be treated very precisely and no systemic effects occur. Finally, NIPP treatment requires considerably less equipment and is therefore much less expensive [63]. A prerequisite for the use of NIPP, however, is the reachability of the affected tissue sections. This poses a certain challenge in the treatment of RCC. In principle, the intraoperative use of endoscopic or laparoscopic techniques is therefore conceivable. However, to verify and further develop this is subject to future studies. Currently, there are no clinical data available.

4. Conclusion

In summary, NIPP treatment has great potential to enhance and supplement existing RCC treatment options. Outstanding characteristics of NIPP treatment are 1) a precise and local effect on the treated tissue and 2) an almost exclusive effect on treated tumor cells without side effects. This allows an enormously large therapeutic window and makes the combination of NIPP treatment and classical therapy appear particularly promising. In addition to RCC, plasma oncology offers an extremely innovative physical treatment method for future oncology in general.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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