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Clinical Studies Applying Physical Plasma in Head and Neck Cancer - Key Points and Study Design

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Abstract

Cold atmospheric pressure plasma (CAP) is known to very effectively inactivate multi-resistant strains of microorganisms. Whether or not application of CAP also inactivates cancer cells is a matter of intense clinical interest. There is a need for prospective, randomized, blindly evaluated clinical trials. This paper outlines the key points of such a study program.

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Introduction

Plasma medicine using cold atmospheric pressure plasma (CAP) -an ionized gas rich in active components, such as radicals and reactive oxygen species– is gaining rapidlyrising attention in cancer treatment research. Numerous in vitro and in vivo tests have unveiled the effectiveness of CAP not only in decontamination of infected wounds and the stimulation of wound healing, but the impact of CAP on cancer cellsas well[1,2,3]. As was recently mentioned by our group in a call for clinical trials [4], CAP is nearing the final stages of development for broad clinical applications in curative and palliative treatment of head and neck cancer.

Despite a series of well observed clues that CAP might serve as a promising tool in cancer therapy, there are still many aspects that remain uncertain. It is therefore important to implement clinical trials to gather more knowledge about the possible benefit of applied plasma medicine in cancer therapy.This agenda aims to collect some of the main topics that upcoming research must focus on and offers strategic key points for setting up clinical studies on head and neck cancer treatment with CAP.

Study Design

Clinical trials with the aim to investigate the benefit of CAP applied in cancer patients need a prospective, randomized, multi-center protocol with an outcome assessment that is blinded and evaluated remotely. Intra-individual protocols are preferable, i.e. areas of tumor surfacetreated with CAP compared with those left without CAP in the same patient, within the highest standards of patient care in a research trial.

Type of plasma source

CAP can be generated by different methods [2]. This leads to a variety of plasma sources and medical devices with different types ofarchitecture, working gases,discharge, energy yield and geometric factors. Due to the need of adequate sample sizes and truly comparable results especially in multi-center studies, it is important to standardizethe study protocol by defining and agreeing upon aplasma source to be commonly used, that has been well studied in pre-clinical trials. Moreover the plasma source has to be suitable for use on clinical features of the tumor under investigation and the instrument itself should be easy to handle from the surgeon´s point of view. In the case of head and neck cancer, presenting mainly open ulcerations with massive bacterial contamination, medical devices in the shape of plasma jets like kINPen MED (neoplas tools GmbH, Greifswald, Germany)are preferable because of their lancet-like plasma tip that offers easy access to the extremely uneven surfaces of this kind of tumor.

Type of cancer

Squamous cell carcinoma samples offer several advantages for the use in CAP-trials: they areopen, visible, solid surfaces which are easy to reachand easy to observe clinicallyover a significant period of time. And they may not be as difficult as other cancersto harvest specimens periodically from the same source if needed for direct analysis of effects and follow up therapy. Moreover, there aresomepre-clinical data and case reports for CAP treatment of this type of cancerpreviously published that can be used for scientific estimation and comparison [5].

Study Hypotheses

The main intention of the clinical study program is to confirm or refute recent findings that lead to three promising study topics: the application of CAP is reducing the,(1) microbial contamination of infected tumor surfaces and the,(2) growth of cancer and therebyis,(3) of benefit for the cancer patient suffering from head and neck squamous cell carcinoma.

Decontamination of infected tumor surfaces

Broad evidence shows CAP's ability to reduce the bacterial load of cancer ulcerations, particularly by decreasing the number of anaerobe species, but a total removal of bacteria was notyet achieved by CAP. New trialsare neededto determine the microbiological aspects, specifically to differentiate between detectable pathogenic species and the extent of measurable reduction that can be achieved with CAP. This knowledge will help increase the efficiency of decontamination.

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Reducetumor growth

When aiming for curative treatment of malignant tumors, the target is the malignant stem cells that initiated clonal tumor growth and maintain the basic development of cancer disease [6]. Clinical observations and findings of immunological interactions [5, 7, 8,9, 10] showed CAP had a significant effect on cancer cells of several tumor lines and tumor models *in vitro* [11]. Its selectivity for cancer cells could lead to a paradigm shift in cancer therapy [12]. However, tumor surfaces exposed to CAP *in vivo* do not show instant local destruction, but only a partial remission after two weeks. Visible effects of CAP (e.g. flattening and arresting of granulomatous proliferations) were observed on treated tissues, but the effectswere irregular where some parts remained in a progressive disease state. Many more standardizedtrials are needed toprove if CAP has a reproducible anti-cancer effect and clarify why there may have previously been an inhomogeneous cellular response.

Patient benefit

Clinical experience with head and neck cancer shows that patients appreciate treatment with CAP – at least in palliative care. By decreasing the load of anaerobic bacteria, CAP also reduces the typical fetid odor of cancer ulcerations. Furthermore, many patients submitted fewer requestsfor pain medication when treated with CAP. The reported amount of pain reduction varied between patients and usually faded out when CAP-treatment was completed. Further research would help to individualize the prescription of drugs by differentiating between responding and non-responding patients. Based on patient surveys and more general knowledge about patient acceptance [13, 14], CAP-therapy could become a well-accepted adjunct to traditionalanti-cancer therapies.

Like other medical procedures application of CAP shows some adverse effects. Patients reported a bad taste after intraoral use of CAP, stinging pain or collateral edema. New trials should help optimize the plasma jet for clinical use and provide information about negative side effects and risk factors.

Competing Interests

The author declares that he has no competing interests.

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