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Short Communication

Non-invasive physical plasma as an innovative physical approach for the oncological therapy of skeletal sarcomas

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Human osteosarcoma is the most common malignant bone tumor with an annual incidence of two cases per 1 million population. Osteosarcoma account for 60% of all malignant bone tumors occurring in childhood, followed by Ewing's sarcoma [1-3]. In adults, however, chondrosarcoma is the most common primary bone malignancy. The prognosis of skeletal tumors depends on their localization, histological typing, and the degree of metastasis. The therapeutical set-up is oriented toward these modalities and for osteosarcoma and Ewing sarcomas consists of preoperative, neoadjuvant chemotherapy, surgical tumor resection, and postoperative, adjuvant chemotherapy. With current therapies, the recurrence-free overall 5 - year survival rate is approximately 60% [4-6]. In contrast, surgical resection is the treatment of choice for chondrosarcoma due to its phenotypic characteristics and resistance to chemotherapy and radiotherapy [7]. It is therefore important to look for new options for the treatment of osseous sarcomas. Due to its anti-oncological effect, one such option may be treated with physical plasma [8-10].

Non-Invasive Physical Plasma (NIPP) corresponds to a highly energized gas (≤ 40 °C) and is composed of numerous biologically active species (e.g. reactive oxygen species) [11-13]. In experimental approaches, treatment with NIPP leads to the inactivation of microorganisms and tumor cells. Previous research in the field of oncological plasma therapy has shown significant growth inhibition and induction of apoptosis in cancer cells when treating osteosarcoma cell lines with NIPP [14]. Especially in cases of insufficient tumor resectability, the growth inhibitory effect of NIPP could represent a promising therapeutic option in the treatment of skeletal tumors.

Although already approved for the therapy of skin diseases for a long time [15], the field of plasma oncology is only now developing, which aims at introducing NIPP in the treatment of tumor diseases. The aim is to use the properties of NIPP to inactivate tumor cells in skeletal sarcomas [16-18].

In malignant cells of skeletal sarcomas such as osteosarcoma, Ewing's sarcoma, and chondrosarcoma, mechanisms of intracellular signal transduction are triggered and lead to complex and usually long-lasting cell responses, e.g. programmed cell death [14,19-22]. At the cellular level, NIPP treatment generally led to the activation of redox signaling pathways (e.g. peroxiredoxins), which in turn induced p53-dependent apoptosis in skeletal sarcoma cells [12,19,20]. In osteosarcoma cells, NIPP-induced release of cytokines and interleukins also occurs [23]. As a result, a reduction in cell motility can be observed in osteosarcoma, Ewing's sarcoma, and chondrosarcoma cells [14,19,20]. This would be of particular importance with regard to metastasis processes in tumor treatment. NIPP treatment has also been shown to increase the permeability of the cytoplasmic membrane of osteosarcoma cells [24]. This property could potentially be used to make chemoresistant tumor cells chemosensitive again by NIPP. Furthermore, NIPP also inhibits tumor-associated angiogenesis [25].

Recent studies have also shown that the specific NIPP effects on osteosarcoma cells depend both on the skeletal sarcoma cell type to be treated and on the NIPP devices used [26]. In practical use, therefore, the specific treatment time (the specific "dose") would first have to be determined and defined. Pharmacologic and radiation therapy can be based

on chemical-physical parameters defining a dose (e.g., mg/kg body weight, total dose in Gy). Although reactive oxygen species are the main factors of biomedical NIPP efficacy, concentration data cannot be used for dosing. On the one hand, the identification of reactive species as well as the determination of their concentrations is analytically complex and not feasible in a clinical context. On the other hand, reactive oxygen species are unstable and react or degrade within split seconds, so composition and concentration are constantly varying [11,13,27].

As a remedy, it has therefore become accepted to specify the duration of NIPP treatment to describe the dosage. This determines the biomedical effect. However, the efficacy is dependent on the NIPP device applied and the tissue treated. While skin and skin cells are comparatively robust to NIPP treatment, other tissues are much more sensitive. Even with cells from the same tissue but of different origins, e.g. tumor cells of the same malignancy but from different patients, significantly different sensitivities can be observed [28].

Furthermore, the efficacy and therefore the dosage also depends on the measured read-out. In the case of plasma oncology, the determination of cell growth has become established. Apoptotic or motility inhibitory effects can also be measured. If NIPP is used to promote wound healing, proliferation and cell motility are often determined. Here, the secretion of anti-inflammatory and regenerative cytokines and chemokines can also be measured [29].

An outstanding medical property of NIPP is its local and overall tissue-preserving effect on the treated organ areas. Cells are devitalized mainly by apoptotic mechanisms and consecutively replaced by neighboring healthy cells of the tissue. These processes lead to regeneration and repair processes that largely preserve the functionality of the treated tissue [29-32]. Furthermore, neither side effects nor treatment resistance that could limit NIPP use has been described so far. This also applies to the strong anti-inflammatory and antimicrobial properties of NIPP. Here, previous studies have also failed to demonstrate any adaptation or resistance effects [28,32-34]. Due to the chemically very reactive oxygen species, the first studies on NIPP technology already tested the extent to which DNA oxidation could lead to genotoxic effects. However, to date, a large number of studies with a wide variety of genotoxic tests have provided no evidence that NIPP can lead to mutations and genotoxicity [35-38]. Finally, current developments show that NIPP can be used at a very low cost. The initial cost is comparatively low, ranging from a few EUR 1,000 to a few EUR 10,000, depending on the manufacturer. The running costs are even negligible, since no reagents and, as a rule, no disposable components are used.

However, these undoubtedly advantageous features of NIPP therapy are offset by limitations. Unsatisfactory is the already discussed lack of a clearly defined dose for NIPP treatment. This complicates the replication and transferability of the therapeutical procedure. Furthermore, the low penetration depth and local effect on tissue may also be detrimental in some applications. It is therefore conceivable that NIPP should be combined with other procedures such as surgical or pharmacological interventions in future applications.

In summary, it can be said that the exposure of cancer cells to NIPP induces numerous cellular responses and leads to the induction of anti-oncogenic effects such as growth and motility inhibition, apoptosis, and changes in tumor-environment interactions. For application in clinical oncology, the cellular and molecular characterization of these effects is essential. Plasma oncology opens up new possibilities for the treatment of skeletal sarcomas as well as for oncological surgery as a whole. As an additional intraoperative option, both the direct treatment of malignant tissue and the treatment of resection margins could become promising options in cancer surgery. The efficacy of NIPP treatment is not only limited to the inhibition of cell growth but also includes other pro-therapeutic effects such as microbial decontamination, immune stimulation, and promotion of wound healing and scar formation.

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