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Content of the commission and purpose of the report

Assessment of the possible influence of ethylenediaminetetra(methylenephosphonic acid) on the development of osteosarcomas: The task of the expert opinion was to present the state of knowledge on the influence of external factors on the development of osteosarcomas in humans and, against this background, to assess the possible effect of ethylenediaminetetra(methylenephosphonic acid) and its salts on the development of osteosarcomas. The corresponding expert opinion was prepared impartially and to the best of our knowledge and belief,

In particular, the following questions were to be addressed at the request of the client:

1 -What causes genetic modifications that lead to the triggering and development of osteosarcomas? For example, are there certain risk groups that are genetically predisposed? Is this also transferable to rats, mice, etc.?

2 -Which chemical structures or which structural characteristics of chemical substances can be considered as triggers for cancer, especially osteosarcomas?

3 -Is anything known about the mode of action of the chemical substances that have been shown to be involved in the development of osteosarcoma?

4 -Which properties of EDTMP are particularly important from a pharmacological, biochemical and medical point of view?

5 - Are the genotoxicity tests carried out sufficient and conclusive and prove that EDTMP does not lead to gene modification, or are the doubts raised justified?

6 -What additional tests do you think are needed to obtain certainty about the pharmacological and biochemical properties of EDTMP in this context?

7 - Are the animal experiments in this form really transferable to humans?

Answers and assessment of the situation

Background to osteosarcoma

Osteosarcoma is the most common primary bone tumor in humans, but with an incidence of 2-3/million/year, it is still a very rare disease. It mainly affects adolescents and young adults and in these mainly the metaphyses of the long tubular bones. Tumors of the trunk or craniofacial localization occur mainly in older adults. The tumour is characterized by a very pronounced tendency to metastasize, which predominantly affects the lungs, less frequently the skeleton and even more rarely other regions of the body. In the past, the prognosis of osteosarcoma was considered to be almost fatal after local therapy alone, usually amputation of the affected limb. Today, the treatment of choice is a combination of local surgery and systemic chemotherapy, which can permanently cure 60% to 70% of tumors that have not yet metastasized (BEIRD 2022).

Answering the questions

Ad 1a: What causes genetic modifications that lead to the initiation and development of osteosarcomas?

Introduction

According to current knowledge, the vast majority of all osteosarcomas occur sporadically and without identifiable causes (BEIRD 2022, BIELACK 2016, OTTOVIANI 2009). Nevertheless, there are some predisposing factors that can or, in individual cases, must be associated with its development.

Genetic predisposition factors

Genetic factors that can lead to the development of osteosarcomas can be congenital ("tumor predisposition syndromes"). The best-known example is probably retinoblastoma, an eye tumor of infants caused by congenital RB1 mutations, which usually occurs very early in infancy and is often congenital and frequently bilateral. Patients with retinoblastoma have an approximately 500-fold increased risk of also developing osteosarcoma (HAMEED 2018, MOLL 1997, TURAKA 2012)

However, the best known and probably most common genetic syndrome that predisposes to osteosarcoma is the so-called Li-Fraumeni syndrome, which is caused by congenital mutations of the p53 tumor suppressor gene (MAI 2017, KRATZ 2017). Such mutations can lead to the development of various malignant solid tumors and, to a lesser extent, to the development of hematological neoplasms. Osteosarcoma is clearly the most common solid tumor promoted by the syndrome in young people.

A number of other congenital genetic syndromes can also favor the development of osteosarcoma, e.g. due to helicase defects. These include Rothmund-Thompson syndrome, caused by RECQL4 mutations, Werner Progerie syndrome with WRN mutations and Bloom syndrome with mutations in the BLM gene, which also codes for a RecQ helicase (HAMEED 2018).

In summary, there are various congenital genetic syndromes that can promote the development of osteosarcoma. According to current knowledge, a total of 10% - over 20% of all osteosarcoma patients are probably affected by such genetic predispositions (MIRABELLO 2020).

Radiation exposure

Genomic alterations associated with osteosarcoma development can also be triggered by physical influences on the genome - radiation exposure - or chemical influences on the genome - alkylating substances (REULEN 2021).

Radiation exposure of the bone, especially but not exclusively at the time of an individual's main growth spurt, has been confirmed as a predisposing event for osteosarcoma (CARUSO 2019, LE VU 1998, OTTOVIANI 2009, PATEL 2000). The "linear dose, no threshold" hypothesis presumably applies here, i.e. any radiation exposure, no matter how small, increases the risk of osteosarcoma; the risk increases linearly with the dose.

Two historical examples of "internal" and "external" radiation exposure will be mentioned to illustrate the possibility of radiogenic facilitation of osteosarcoma development:

1. "Radium Girls": in the early 20th century, for example, the luminous hands of watches were made to glow by painting them with radium, a radioactive element. The radioactive paint was applied by young ladies, the so-called "radium girls". They subsequently developed a high incidence of craniofacial osteosarcoma (CLARK 1997).

2. Hiroshima and Nagasaki: A significantly increased incidence of osteosarcoma was later found among the survivors of the atomic bombings of Hiroshima and Nagasaki (SAMARTZIS 2011).

However, radiation exposure through therapeutic radiation is more common today than accidental radiation exposure. The risk of osteosarcoma induction exists on the one hand, relatively speaking, to a lesser extent through external diagnostic radiation exposure (e.g. X-ray examination, computer tomography), and on the other hand to a greater extent through therapeutic radiotherapy, as is used in cancer therapy in particular. The risk of osteosarcoma developing increases with increasing radiation dose and the increasing volume of the irradiated bone area. Well-known examples of the not entirely rare radiation-induced osteosarcomas (BIELACK 1999) are, for example, secondary osteosarcomas after radiotherapy for Ewing's sarcoma (BIELACK 2023) or secondary thoracic osteosarcomas after radiotherapy for breast cancer (NOH 2012, RIBEIRO 2023).

Hormones

An increase in the risk of osteosarcoma due to growth hormone application and variations in estrogen metabolism (MUSSELMAN 2012, POIDVIN 2018) during the phase of incomplete body growth is considered at least possible to probable. This can be indirectly explained by the fact that bone growth can generally be linked to the risk of osteosarcoma (GIANFERANTE 2023). Hormones that do not influence growth are not associated with the development of osteosarcoma.

Growth

In addition to the external supply of growth hormone, a person's longitudinal growth is also indirectly dependent on their genetic constitution. People who exhibit increased body growth generally have a moderately increased risk of developing osteosarcoma, regardless of the reason for this (GIANFERANTE 2023, TROISI 2011). Not only the rare giant growth syndromes are affected here. This is made clear, for example, by the fact that boys - on average taller than girls - have a higher risk of osteosarcoma in comparison (ratio around 60%:40%) (BEIRD 2022). The peak age of incidence also occurs a few years earlier in females than in males, correlating with the slightly earlier main growth spurt in girls (BEIRD 2022). In addition, osteosarcoma in young people occurs preferentially in precisely those regions of the body that grow particularly strongly during puberty: distal femur, proximal tibia and proximal humerus are the three main sites of manifestation in young people of growing age (BEIRD 2022). However, once longitudinal growth is complete, the proportion of osteosarcomas of the trunk increases sharply and becomes similar to that of osteosarcomas of the extremities (BIELACK 2023, DUCHMAN 2015, FERRARI 2018).

Other chemical substances

An increase in the risk of malignancy due to alkylating substances can generally be considered certain (ZAHNREICH 2021). This probably also applies to sarcomas as a group, including osteosarcoma. However, the risk of myelodysplastic syndromes and acute myeloid leukemia induced by alkylating

substances must be classified as much higher (MORTON 2019). An isolated increase in the risk of osteosarcoma is not to be expected from alkylating substances.

In recent years, based on rat models, a possible influence of the recombinant human parathyroid hormone (PTH) teriparatide on the incidence of osteosarcoma has been reported. Current analyses conclude that the application of teriparatide is not linked to the incidence of osteosarcoma (ABDULELAH 2023, GILSENAN 2021). A corresponding warning about this previously suspected risk in the US approval text was therefore removed (KREGE 2022).

To date, it has not been clearly demonstrated that exposure to other (non-radioactive) substances can have a positive or negative influence on the development of osteosarcoma.

Ad 1b: Are there, for example, certain risk groups that are genetically predisposed?

As can be seen from 1a, osteosarcoma occurs more frequently in certain genetically predisposed people than in the reference population. A distinction must be made here between the congenital osteosarcoma predisposition syndromes mentioned above, often in the context of more extensive cancer predispositions, and the acquired osteosarcoma risks.

Ad 1c: Is this also transferable to rats, mice, etc.?

In principle, according to current knowledge, the above also applies to animals. However, the significance that various influences can have on the development of osteosarcoma varies greatly depending on the species (GUIJARRO 2014).

Ad 2: Which chemical structures or which structural peculiarities of chemical substances can be considered as triggers for cancer, especially osteosarcoma?

It should be clear from the above under 1a that alkylating substances in particular can be held responsible for the development of cancer in general and thus probably also for sarcomas, including osteosarcomas. However, it must be emphasized once again that the influence on leukemogenesis must be estimated to be many times higher.

(It must be noted here that the expert is not a chemist and his knowledge of the chemical structures of certain substances is not nearly comparable to that of a chemist).

Ad 3: Is anything known about the mode of action of the chemical substances that have been proven to be involved in the development of osteosarcomas?

Chemical substances that have alkylating properties can increase the risk of developing osteosarcoma (presumably, see above).

Chemical substances that directly or indirectly lead to an increase in bone growth can increase the risk of developing osteosarcoma (confirmed, see above).

Chemical substances that are radioactively labeled can increase the risk of developing osteosarcoma (confirmed, see above).

Ad 4: Which properties of EDTMP are particularly important from a pharmacological, biochemical and medical point of view?

In connection with the possible promotion of later bone tumors, the clear accumulation of EDTMP in osteoid, i.e. immature bone, should clearly be mentioned here. In this way, bone remodeling processes can be visualized and, ideally, influenced. This is utilized in both diagnostic and "therapeutic scintigrams", e.g. with 153SmEDTMP (153-samarium ethylene diamine tetramethyl ethylene phosphate) (MURRAY 2021, SMITH 2021). In each case, a radioactive tracer is bound to the phosphonate, which preferentially accumulates in immature bone as a result of this binding. Various bone remodeling processes can be visualized in this way, which is widely used in nuclear medicine (not only for malignant bone processes). Therapeutically, this effect is used, for example, for local irradiation of bone metastases, especially in prostate cancer (MURRAY 2021). It should be noted that the phosphonate is only used because of its accumulation in the bone. It is not therapeutically effective itself. The actual irradiation is carried out by the radioactive tracer bound to it.

Ad 5: Are the tests carried out on genotoxicity sufficient and conclusive and prove that EDTMP does not lead to the alteration of genes, or are the doubts raised justified?

As a professional and scientifically clinically active person, I cannot answer this question with sufficient certainty. However, the medical indications known to me in which non-radiolabeled EDTMP is used have not, to my knowledge, given rise to any concern that the substance may have carcinogenic potency in humans.

Ad 6: In your opinion, what additional tests are required to obtain certainty about the pharmacological and biochemical properties of EDTMP in this context?

From a clinical point of view, I cannot see any need for additional tests in this context.

Ad 7: Are the animal studies in this form really transferable to humans?

Animal experiments on osteosarcoma are probably (only) partially transferable to humans. However, they are carried out time and again, sometimes in the absence of more suitable, better models. It should be noted that the epidemiology of osteosarcoma in different animal species is very heterogeneous and in some cases also very different from that in humans (GUIJARRO 2014). Dogs may serve as an example here: In very large dog breeds, osteosarcomas are not - as in humans - among the very rare cancers, but among the most common malignant tumors of all. Unlike in humans, they do not occur primarily in the lower extremities - the hind legs in dogs - but in the upper extremities - the front legs in dogs (BECK 2022, JARVIS 2021, MAKIELSKI 2019).

It should also be noted that the lifespans of different animal species vary greatly, which often makes long-term observation and thus the detection of late events impossible. The metastasis pattern of osteosarcomas in different animal species may also differ considerably from each other and from humans (JARVIS 2021). The very strong lung involvement of metastases observed here is by no means found to the same extent in all animal species. Nevertheless, in the absence of other, more suitable alternative models, animal experiments are also a frequently used auxiliary model for osteosarcoma.

Assessment of a possible effect of EDTMP exposure on osteosarcoma development

Direct references to a possible correlation between EDTMP or other aminomethylene phosphonates and osteosarcoma formation have not yet been the subject of published scientific studies. Due to the proven analogy of EDTMP and hydroxy-bisphosphonates in adsorption behavior and chelation, it is permissible to transfer the large number of studies and publications on hydroxy-bisphosphonates to

EDTMP. There is no evidence in the specialist literature that would prove such an association or even causality (HEYMANN 2020).

Summary and evaluation

The incidence of osteosarcoma is low. It varies with various genetic, biological and external influencing factors. The use of non-radiolabeled aminomethylene phosphonates and hydroxy-bisphosphonates has so far not been associated with the incidence of this tumor in humans, despite extensive studies on its occurrence.

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