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Mini Review

Mini Review: Hyperthermia Treatment for Bone Cancers

Justine Katherine Lee and Oana Bretcanu*

School of Engineering, Newcastle University, Newcastle Upon Tyne, UK

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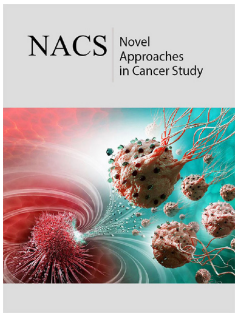

***Corresponding author:** Oana Bretcanu, School of Engineering, Newcastle University, Newcastle Upon Tyne, NE1 7RU, UK; e-mail: oana.bretcanu@newcastle.ac.uk

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Abstract

Treatment of bone cancer usually involves surgical resection of the tumours, as well as the use of radiation or drugs, in order to kill tumour cells and/or prevent further growth and reproduction of tumoural cells. Hyperthermia is a complex method of treatment that involves the use of heat to selectively kill tumour cells. Due to their poorly organised blood system, tumours cannot dissipate heat effectively, leading to cell death via different cellular and molecular modifications of the structure and microenvironment of tumour tissue.

Keywords: Cancer; Bone; Hyperthermia

Introduction

Bone is one of the most common sites for metastasis. Approximately 350,000 people die in the United States every year from bone metastases [1]. The most common site of bone metastases is the axial skeleton, with the lumbar region being the most frequently impacted site [2]. Bone cancer can lead to bone pain, hypercalcemia, spinal cord compression and bone fracture, decreasing the quality of life of cancer patients [3]. The most common treatments for bone cancers are surgical resection, radiotherapy and chemotherapy. Hyperthermia is another type of cancer treatment that is generally used for advanced cancers, in combination with radiotherapy or chemotherapy. Clinical trials have shown that hyperthermia reduces the size of tumours, enhancing the effect of radiation or anticancer drugs [4]. Hyperthermia affects both molecular and cellular levels. Alterations to the cytoskeleton and the cell membrane, as well as impairment of protein, Ribonucleic Acid (RNA) and Deoxyribonucleic Acid (DNA) synthesis, inhibition of DNA repair enzymes, altered gene expression and protein denaturation, unfolding and aggregation [5-7] are all changes caused by hyperthermia.

Discussion

Hyperthermia is defined as 'raising of cancer tissue to 41 °C or higher by external means, with the aim of eradicating active malignant cells to improve cancer control' [8]. Hyperthermia may selectively target tumour tissue due to its microcirculation differences compared to normal tissue. As tumours have a poorly organised and chaotic blood system, they are highly ineffective at dissipating heat [8]. Following the application of external energy (heat), blood vessels within normal tissue dilate, leading to an increase in blood flow and a subsequent reduction in temperature. However, tumour tissue has a chaotic and poorly organised vasculature, and the vessels cannot dissipate the heat (Figure 1), increasing the temperature locally. This leads to activation of molecular and cellular alterations in the tumour, such as inhibition of DNA repair enzymes and denaturation, unfolding and aggregation of proteins, causing cell death via necrosis or apoptosis [5,7]. Additionally, as the microenvironment of cancerous tissue is characterised by a reduction of blood flow and blood vessel density, it favours hypoxia, acidosis and energy deprivation [7]. Therefore, when compared to normal tissue, greater damage is generated in tumours as a result of hyperthermia [9,10].

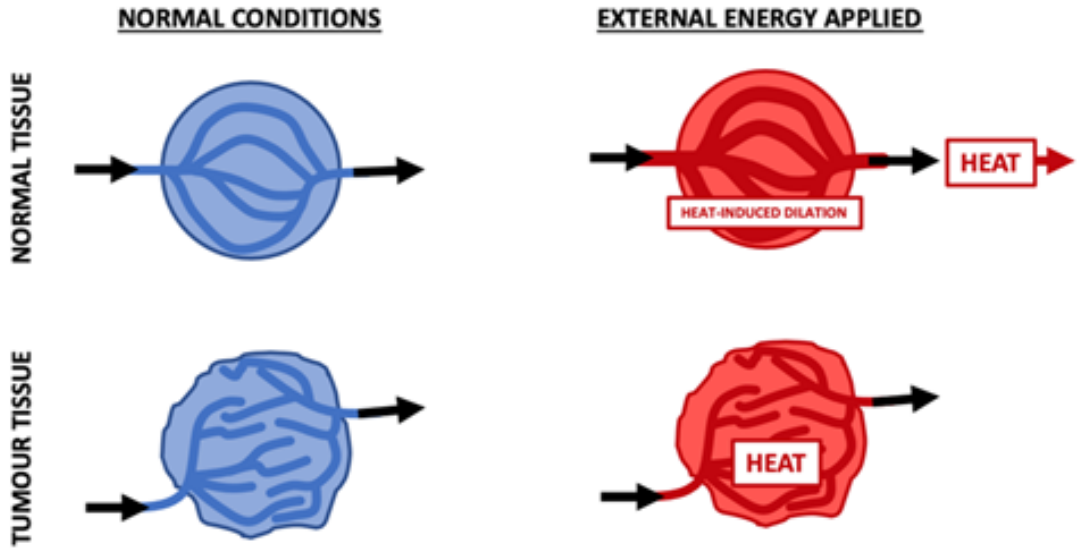

Figure 1: Heat dissipation in normal and tumour tissues (adapted from [10]).

There are two main types of hyperthermia, thermotherapy and thermal ablation. Thermotherapy occurs when heat is used to increase the body temperature to 41-45 °C, with the aim of selectively causing cell death of the tumour, while leaving the surrounding healthy tissue unaffected. Thermotherapy is also able to enhance the therapeutic effect of other cancer treatments, such as radiotherapy and chemotherapy [11]. Conversely, thermal ablation is the use of temperatures above 45 °C in order to cause destruction of cells. This technique can damage both tumour and healthy tissue [11].

While the exact mechanism by which hyperthermia induces cell death is not completely understood, it is thought to be due to a combination of disruptions that occur within the cell [6]. Nevertheless, hyperthermia ultimately leads to cell death via either necrosis or apoptosis [7]. Necrosis (premature cell death) is a passive pathological cell damage that is followed by an inflammatory response, whereas apoptosis is genetically controlled, programmed cell death [7]. Apoptosis can occur via the extrinsic or intrinsic pathways, which differ in the cascade of proteins they activate although both pathways ultimately lead to cell death [5]. However, most of the stimuli that cause apoptosis can also induce necrosis when the cell is subjected to prolonged exposure to heat [7]. It has been shown that some types of cells show varying susceptibilities to apoptosis following heat exposure, although above certain temperatures necrosis is more likely to occur [7].

There are three main categories of hyperthermia: local, regional and whole-body [6,12]. Local hyperthermia is used for solid localised tumours that are at or near the surface, and heating is achieved with the use of external or internal energy sources [6]. Regional hyperthermia is generally utilized when tumours are located in deep-seated tissues or when larger areas of the body require heating. This method usually relies on increased perfusion of organs or limbs through heating of the blood or irrigation of body cavities [6]. Whole-body treatment is used in order to treat metastatic cancer and is achieved with the use of a flexible infrared chamber, a heated blanket, or simply by heating the patient's room [6]. More complex methods have been developed that use approaches such as radiofrequency, microwave, ultrasound techniques and magnetic fields, which can effectively target deep-seated tissues within the body [6,13,14].

The method by which the body temperature is raised is still being improved due to challenges that this cancer treatment poses [15], such as special equipment [4] and its limited ability to directly target the tumour site [13] or to keep a uniform temperature within the target area [16]. The effectiveness of the treatment heavily relies on the duration of the treatment and the temperature obtained [10,17], as it has been demonstrated that even half a degree rise in the temperature within the body can have a substantial effect on cell survival [18]. Therefore, accurate detection is required for hyperthermia to be successful, as well as the ability to maintain the temperature throughout the treatment [6]. For example, at temperatures above 42 °C a reduction in blood flow within the tumour is observed, resulting in impairment of oxygen and nutrient supply, ultimately leading to acidosis. However, at temperatures below 42 °C improvement of tumour blood flow is detected. This causes an increase in oxygen content and subsequently improves the effectiveness of other cancer treatments, such as radiotherapy and chemotherapy [7].

As well as being able to induce cell death as a singular treatment, hyperthermia is commonly used as an adjuvant cancer therapy, due to its ability to enhance the effects of treatments such as radiotherapy and chemotherapy [10,19]. Results from clinical trials have shown that there is improved response and survival rates [7], as well as faster regression rates [20], in patients treated with both hyperthermia and radiotherapy compared to radiotherapy alone. Similar results have been observed in patients treated with

chemotherapeutics in combination with hyperthermic treatment versus chemotherapeutics alone [21,22].

The increased effectiveness of radiotherapy, when heat is applied in conjunction, is most likely a result of an increase in oxygen levels within the tumour. This leads to the facilitation of the formation of radiation-induced oxygen radicals, which produce double-strand breaks in DNA, which may cause cancer cell destruction [23]. Furthermore, the improved efficacy of chemotherapeutics when used in combination with hyperthermia may be due to 'altered drug pharmacokinetics, such as increased solubility, altered binding of plasma proteins and activation of enzymatic processes' [8]. Additionally, it has been demonstrated that hyperthermia negatively impacts the DNA repair mechanisms [8,23], which may play a role in the increased effectiveness of radiotherapy and chemotherapy.

Conclusion

Hyperthermia is an attractive bone cancer treatment due to its lack of severe side effects. It is mainly used as an adjuvant therapy, in combination with radiotherapy or chemotherapy. However, the use of hyperthermia is currently limited by the ability of existing equipment to effectively target deep-seated tumour sites or maintain a homogeneous temperature within the target area. The development of hyperthermia as a treatment for cancer provides an avenue that allows tumour cells to be destroyed, via the production of heat, with minimal side effects. Due to their poorly organised blood system, tumours are more sensitive to heat than normal tissue. Optimised heat treatment can trigger cancer cell death through numerous cellular and molecular alterations. Development of new materials and minimally invasive devices for localised deep-seated bone cancers could unlock the potential of hyperthermia treatment and open it up to wider use.

Conflict of Interest

There is no conflict of interest regarding the publication of this article.

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