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Millimeter Wave and Drug Induced Modulation of the Immune System -Application in Cancer Immunotherapy

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Abstract

In recent years several approaches have been used for the treatment of cancer. These include surgery, chemotherapy, radiotherapy, and immunotherapy. Immunotherapy includes systemic administration of cytokines, adaptive transfer of activated T cells, NK cells, dendritic cells and macrophages. Immunotherapy is used to stimulate and train the patient's immune system to fight against cancer. However, this approach alone is not sufficient. Therefore, a combination of immunotherapy with conventional chemo- and radiation therapy is commonly used for the treatment of cancer. But systemic administration of cytokines, such as interferons and interleukins, commonly used for immunotherapy, have their own toxic side effects that can be life threatening to many patients. In this article, we have reviewed the current knowledge of the effects of millimeter wave therapy (MMWT) on the immune system. MMWT, an alternative and complementary modality of treatment, is widely used for the treatment of cancer and many other diseases in Russia and several East European countries. However, it is virtually unknown to Western physicians. Our experimental studies have shown that MMWT when used in combination with chemotherapy protects the immune system from the toxicity of chemotherapy without introducing any additional toxicity of its own. Furthermore, our studies have shown that the combined millimeter wave- and chemotherapy can reduce the tumor metastasis, and tumor resistance to chemotherapeutic drugs. Thus combined therapy using MMWT provides a promising new strategy for the treatment of cancer.

Keywords: Millimeter wave therapy; T cells; NK cells; Macrophages; NF-κB; Metastasis; Chemoresistance; Apoptosis

Introduction

Millimeter electromagnetic waves (MMWs) are widely used for the treatment of many diseases in Russia, China, and many East European countries [1-6]. The three most common frequencies employed are 42.2, 53.6 and 61.2 GHz. These are approved by Russian Ministery of Health for medical treatment Excellent clinical results have been reported in the treatment of various diseases, including peptic ulcers, pain relief, cardiovascular diseases, wound healing, bronchial asthma, infantile cerebral palsy, skin disorders, chronic alcoholism, diabetic angioneuropathies, and cancer. Based upon some estimates, there are more than 1000 medical facilities in Russia alone where MMW therapy is being used, and the number of patients undergoing medical treatment exceeds 250 thousand per year [1]. In spite of the large numbers of patients treated with MMW therapy (MMWT) in the former Soviet Union, this treatment modality is virtually unknown to Western physicians and scientists. MMWs can be used as a monotherapy or in combination with other treatment methods. As an adjunct therapy, they are widely used to protect the immune system from the toxic effects of chemo- and radiation therapy in the treatment of cancer [3,7].

The usual treatment regimen consists of daily applications of low power MMW radiation for 15 to 30 minutes for 5 to 15 days. The MW device is typically a "book-sized" instrument which is brought in close contact with the skin surface. The site of application varies with the disease being treated. Surface wounds and skin diseases are usually treated at the site of the lesion. In treating arthritis, the site of application is at the affected joint. In treating internal diseases, the recommended site of application may be at any one of a number of anatomic or acupuncture points. A common site of application is the lower end of the sternum [6].

In recent years, several papers have been published on the biological effect of millimeter waves showing an increasing interest in the application, and understanding the mechanisms involved in MMWT [8-13]. In general, the effect of MMWT in clinical applications can be divided into three broad classes: (a) sedative and analgesic effects, (b) anti-inflammatory and repair stimulating action and (c) normalization of the immune system. There are many reports, mostly in the Russian literature, that MMWT produces both nonspecific and specific enhancement of the immune system [14,15]. The changes include an increase in phagocytic activity of macrophages [16], enhanced proliferation and normalization of the ratio of $CD4^+/CD8^+$ T-lymphocytes [17,18], and increased number of B-lymphocytes and normalized production of immunoglobulins [17-19]. It is generally believed that beneficial effects of MMWT in many diseases are due to enhancement of the immune response. In cancer treatment, MMWT has been used as monotherapy or in combination with chemo- and radiotherapy to increase immunity, and to reduce the toxic side effects of the above therapies [3,7,20]. Our experimental studies have shown that MMWT can reduce spread of melanoma metastasis [21]. In this short article, we review the current knowledge of the effects and molecular mechanisms of MMW therapy in protecting the immune functions from the toxic effects of chemotherapy. Specifically, we will discuss the effect of MMWT on T cells, NK cells and macrophage

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functions which constitute the most important cells in the fight against cancer.

Effect of MMWT on the T cell Functions

Our studies have shown that MMWT enhance T cell-mediated immunity. A delayed type hypersensitivity (DTH) assay in mouse skin was used to measure this effect [22]. Development of the DTH reaction in mouse or human skin has been shown to involve antigen-specific, T cell-mediated, memory dependent immunity [23,24]. Furthermore, we have examined whether MMWT can modulate T cell recovery after suppression with cyclophosphamide (CPA), an anticancer drug [25,26]. CPA is an alkylating agent that can prevent cell division by cross-linking DNA, leading to the reduction of tumor growth [27,28]. In addition to its cytotoxic effect on tumor cells, CPA is known to have multiple effects on the immune system resulting in a general depletion of immuno-competent cells [29]. A major side effect of this drug in chemotherapy is suppression of humoral and T cell-mediated immunity [30,31]. Among the problems associated with chemotherapy, restoration of immunocompetence is a critical issue to protect patients from secondary infections [30]. T cells have an impact on practically all aspects of immunity due to their ability to induce specific immune responses in both T and B cells. Also, T cells play an important role in the restoration process.

T cell functioning can be divided into an activation phase in which T cells divide and differentiate; and an effector phase, in which their function is expressed. Several basic effector functions have been defined for T cells: cytotoxic $CD8^+$ T cells, directly kill infected cells, while, $CD4^+$ -helper T (Th) cells can activate either B cells or macrophages in ways that are determined by the cytokines they produce. Pro-inflammatory cytokines, produced by Th1 cells, such as IFN-γ, activate, macrophages.and cytotoxic T cells; anti-inflammatory cytokines such as IL-10 produced by Th2 cells activate B cells. Our studies have shown that MMWs can restore production of IFN-γ and proliferation of T cells suppressed by CPA treatment. Conversely, no significant changes were observed in the level of IL-10 and proliferation of B cells. These results suggest that MMWs accelerate the recovery process selectively through a T cell-mediated immune response [25,26].

T cells play an important role in defense against tumor cells. Tumor cells can suppress functions of dendritic cells and macrophages thereby causing them to be incapable of stimulating and activating T cells sufficiently [32]. Considering the importance of these cells, clinical studies related to immunotherapy with activated T cells have been performed for various tumor types with promising results [33-35]. In view of our studies that MMWs can restore functions of T cells suppressed by chemotherapy, combined therapy should be very useful in cancer treatment.

Effect of Millimeter Wave Radiation on Natural Killer Cells

NK cells are known to kill a wide variety of tumor cells while sparing normal cells [36,37]. NK cells represent a distinct population of lymphocytes in terms of both phenotype and function [38]. They have large granular lymphocyte morphology and express characteristic cell surface receptors, such as the NK cell receptor protein-1 (termed NK1.1). NK cells mediate resistance to viral infections and cancer development and exhibit cytotoxic activity, which is nonrestricted to MHC (major histocompatibility complex) [39,40]. Thus, NK cells represent major effector cells of innate immunity. In addition, NK cells possess a variety of other functions, including the ability to produce a number of cytokines, involved in the modulation of hematopoiesis, immune responses and in the regulation of their own activities [41-43].

Our studies [44] have shown that treatment of mice with CPA, an anti-cancer drug, resulted in a significant suppression in cytolytic activity of NK cells. It was interesting to observe that irradiation of CPA treated mice with MMWs, accelerated the recovery of NK cell activity. It was further demonstrated that MMW irradiation significantly augment TNF-α production by NK cells suppressed by CPA administration. This observation supports the idea that the immunomodulatory effect of MMW irradiation could be beneficial when used in combination with chemotherapy. Similar results on the effect of MMWs on NK cell activity were reported by Novoselova et al. [15] who studied the effect of MMWs on the immune system in mice with experimental tumors. MMW irradiation caused a significant increase in the production of TNF-α, nitric oxide and NK cell activity at the early stage of tumor development. MMW irradiation has also been shown to restore splenic NK cell activity suppressed by painful electric stimulation of the hind limbs in rats [45].

Several NK cell based immunotherapies have been developed in recent years [46], These include activation of a Patient's NK cells by injecting different cytokines such as IL-1,IL-2, IL-12 IL 15, and IL-18 etc. Most commonly, IL-2 has been used for immunotherapy. It enhances NK cell-mediated IFN-γ production. The antitumor effect of IL-12 and IL-18 are also associated with upregulation of IFN-γ production by T cells and NK cells. IFN-γ has been shown to suppress tumor angiogenesis, and induce apoptosis in a variety of tumor cells by activating death receptors of the TNF super family. These include mainly FAS ligand receptors and TRAIL receptors [46]. However there are several limitations in the use of cytokines given exogenously for cancer treatment. Toxicity of systemic cytokine administration, and cytokine activated apoptosis of NK cells are two major limitations of cytokine mediated immunotherapies. Studies by us and others have shown that irradiation with millimeter waves increase the production of IFN-γ, TNF-α, IL-2 and enhance the cytotoxic activity of NK cells *in vivo* [44]. Therefore, immunotherapy by MMW should offer an advantage over the cytokine therapy given systemically. However, further experimental and clinical studies are needed to confirm this finding.

Effect of Millimeter Waves on Macrophage Functions

Macrophages are large mononuclear phagocytic cells important in innate as well as in cell mediated immunity. Macrophages play a critical role in host defense against microbial invasion and tumor cells. Macrophage activation is important in controlling of many key processes of immune system. When activated, macrophages are known to produce reactive oxygen and nitrogen species, free radicals, and TNF-α. TNF-α was first described as an endotoxin-induced and macrophage secreted factor that caused hemorrhagic necrosis of tumor cells. TNF-α is now recognized as a critical cytokine orchestrating cell differentiation, activation, proliferation and survival [47-50].

Our studies have demonstrated that CPA treatment of mice causes a strong decrease in spontaneous release of TNF-α by peritoneal macrophages that was restored to normal level when animals were irradiated with MMWs [26]. Several studies have shown that millimeter waves can activate macrophages [51]. The role of activated macrophages in the defense against tumor cells and in cancer treatment has been studied extensively [52]. It has been reported that macrophages can

be involved in tumor cell killing, as well as in stimulation of tumor development and metastasis [53]. Activated macrophages are able to recognize, bind, and subsequently kill tumor cells. They can distinguish between tumor and normal cells based on differences in cell composition. Several studies have shown that a higher concentration in the amount of phosphotidylserine (PS) in the outer membrane of tumor cells is one of the factors responsible for specific tumor cell recognition and lysis or phagocytosis of tumor cells [52]. It has been shown that MMW irradiation can cause externalization of PS in the outer layer of membrane leading to apoptosis [54]. Since the rate of apoptosis depends upon the concentration of PS in outer layer of the cell membrane [55], MMWT holds a great potential to preferentially kill tumor cells because of greater accumulation of PS in their cell membrane.

Inhibition of Drug Resistance by MMWs

A major problem in cancer therapy is the development of tumor resistance to chemotherapeutic drugs. The major culprit involved in the development of drug resistance is the nuclear factor NF-κB, a transcription factor, that is involved in regulation of several genes. Many studies have shown that antineoplastic agents themselves can enhance this resistance through induction of NF-κB. There is ample evidence to indicate that both constitutive and inducible activation of NF-κB can protect tumor cells from apoptosis and thus enhance chemoresistance [56-58]. The above reports suggest that agents that inhibit activation of NF-κB by chemotherapeutic drugs may also inhibit tumor resistance to chemotherapy. In support of the above hypothesis, it was shown that inhibition of inducible NF-κB activity reduces tumor resistance to chemotherapy [59,60].

Our studies have shown that MMW irradiation can inhibit activation of NF-κB induced by CPA, an anticancer drug [61]. These results suggest that MMW therapy when applied in conjunction with chemotherapy can reduce tumor resistance to the antineoplastic agents. The mechanisms through which MMWs inhibit drug induced activation of NF-κB remain to be elucidated.

Inhibition of Tumor Metastasis

One of the major side effects of chemotherapy is that although anti-cancer agents can reduce the growth of primary tumors, paradoxically, they may also enhance tumor metastasis. At the commonly used doses, most anticancer agents are immunosuppressive and therefore secondary neoplasias may result. For example, it has been reported that CPA can enhance tumor metastasis [62,63]. A recent study suggests that paclitexal, a drug curretly used for many forms of cancer might also increase metastasis [64]. It has also been shown that many antineoplastic agents including CPA can reduce NK cell activity [65,66]. Furthermore, it has been demonstrated that a reduction in NK cell activity results in enhancement of tumor metastasis [67-69]. Since our studies have demonstrated that the CPA induced suppression of NK cell activity can be restored by MMW therapy [44], we have further examined whether MMWs can also inhibit the enhanced tumor metastasis resulting from CPA pretreatment. In order to test this further, we used an 'experimental metastasis' model in which B16 melanoma cells were injected intravenously into C57BL/6 syngeneic mice and tumor development was evaluated in the lungs. The result of our studies showed that MMW irradiation at 42.2 GHz can reduce the metastasis enhanced by CPA treatment, suggesting that a combination of MMW- and chemotherapy can provide a promising new strategy to reduce metastasis in cancer treatment.

Molecular Mechanisms of MMW Treatment

We believe that biological effects of MMWs (penetration depth less than 1 mm in skin) are initiated by activation of free nerve endings in the skin [70-73]. Then the signal is conveyed to the central neural system where it modulates neural activity resulting in the development of various biological effects, such as the release of endogenous opioids. In support of this, it was shown that hypoalgesic effects of MMWs were abrogated when animals were treated with naloxone, a nonspecific blocker of opioid receptors, prior to MMW irradiation [74]. Furthermore, the involvement of endogenous opioids in suppression of melanoma growth by MMWs has also been reported [75].

In several studies from our group, it has been shown that MMW irradiation can induce release of endogenous opioids [76]. There is sufficient evidence that opioid peptides can modulate the immune system. The target of the effect of endogenous opioids could be NK cells [77], cytolytic functions of cytotoxic T cells, and the balance of Th1 and Th2 cytokines [78]. The disruption of a normal Th1/Th2 balance occurs in various immunological diseases [79,80]. In a recent study, we have reported that immunomodulation of T cells by millimeter waves is mediated by endogenous opioids [81]. However further studies are needed to determine whether endogenous opioids are involved in the observed effects of MMWs on the other components of the immune system suppressed by drug treatment. A systematic study on the combined effect of CPA and MMW on cytokine release in the presence or absence of naloxone and selective opioid receptor antagonists would be helpful in delineating the mechanisms involved in protection of immune functions by MMWs.

Conclusions and Perspectives

The studies reviewed above, suggest that MMW therapy may serve as an adjunct therapy to protect innate and adaptive immune functions from the adverse effects of chemotherapy in the treatment of cancer. Further in depth mechanistic studies in animal experiments and clinical trials, are needed to fully appreciate the value of millimeter wave therapy in combination therapy of human cancers. Specifically, more preclinical studies need to be conducted to investigate the effect of MMWT on regulatory T cells, tumor cell growth, tumor apoptosis, tumor microenvironment, and tumor angiogenesis. In addition, the effect of MMWs on inflammatory enzymes which have been shown to enhance tumor growth and metastasis (e.g. cyclooxygenase 2, and metalloprotein-9) needs to be further investigated. The results of these studies will provide a scientific rationale for Western physicians to perform clinical trials in cancer patients.

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