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Ultrasound Irradiation for Human Cancer

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Ultrasound (US), which is routinely used for diagnostic imaging applications, is now being adopted in various therapeutic applications. Recent studies showed that low-intensity US irradiations enhanced the anti-tumor effect of anti-tumor drugs or chemotherapeutic agents in vitro and in vivo [1,2]. The human leukemia cells were shown to be selectively eliminated by low-intensity US in the presence of photosensitive drugs [3].

Angiogenesis, the growth of new capillary blood vessels from pre-existing vasculature, is a crucial process for tumor progression and metastasis in cancer. The microvascular endothelial cells (ECs), which are recruited by tumors, have thus become an important second target in cancer therapy [4]. Angiogenesis inhibitors have thus been developed to target vascular ECs and block tumor angiogenesis. Anti-angiogenic therapy was shown to be able to suppress tumor growth in various cancers in vivo, and their following clinical trials have shown successful results for advanced cancers in colorectum, lung, kidney, breast, and ovary. The addition of antiangiogenic agents to chemotherapy has been shown to potentially increase clinical efficacy without severe side effects in most clinical trials, thus the anti-angiogenic approach can be a chief method in modern cancer therapy. Recent studies have reported that the combination of low-intensity ultrasound irradiation and anti-angiogenic agents, or low-dose anti-cancer drugs, which act as anti-angiogenic manner successfully showed synergistic anti-tumor effects for highly aggressive human sarcomas in vivo [5, 6].

The mechanism behind the augmentation of the activity of anticancer drugs and other agents by low-intensity US remains to be fully elucidated, however, several mechanisms have been suggested: 1) Increased permeability; increased intracellular concentration of drugs after ultrasonic irradiation suggests an increased permeability (also called sonoporation, or the opening of pores in the cells. Sonoporation is the term used for the phenomenon by which ultrasound may transiently alter the structure of the cellular membrane, thus inducing an enhanced uptake of low and high molecular weight molecules into the cell. Sonoporation (transiently increased permeability of cell membrane), and resealing of cell membrane by acoustic pressure are considered to be a primary reason for an increased intracytoplasmic concentration of the administered agent [3]. A direct observation of the cells by electron microscopy has been shown to confirm the presence of pore-like disruptions in the cell membrane after the combined treatment. Regarding the mechanisms of action in vitro environment, acoustic cavitation and streaming may be predominated. The potentiation of the agent; some anticancer agent may become more potent against the tumor cells when they are used in conjunction with US. The absorption of US energy by the agent and production of free radicals are seemed to be the likely mechanisms of this increase. 2) Increased sensitivity of the cells to the agent; US alone can cause lethal or sublethal cellular damage. Interestingly, current studies have shown that US alone could inhibit the growth of human cancer xenografts established from highly aggressive malignant tumors [5,6]. In these histopathological results, the destruction of tumor vessels and area of coagulative necrosis were apparently seen in tumors of either US therapy alone or combination treatment of US and anti-angiogenic agent, thus suggesting direct cellular damage by US irradiation. One commonly observed vascular effect, usually characterized by an increased tumor blood flow during initial period of therapeutic US irradiation and eventual destruction of the vasculature, renders the tumor mass more hypoxic. The other studies showed that malignant cells were found to be sensitive to therapeutic US treatment, thus resulting in a transient decrease in cell proliferation. In a suspension of carcinoma cells exposed to 1 MHZ ultrasound, cell killing was induced, accompanied by DNA strand breaks. This might be mainly attributable to free radical formation and the pyrolyitic processes. Sublethally damaged cells by US are thus suggested be more biologically susceptible to the anti-tumor agents. 3) Potentiation of the agent; it is also suggested that anticancer agents became more potent against the tumor cells when they were used in conjunction with US. The absorption of ultrasound energy by the agent and the production of free radicals have been cited as the likely mechanism of this increase. Inertial cavitation is required in this process, primarily in the production of free radicals. Recent in vivo studies showed that the irradiation with low-intensity US within a few minutes after the subcutaneous injection of anti-cancer agent or anti-angiogenic agent may accelerated the drug potentiation, especially in the agents having short mean plasma half-life within 10 min in humans by intravenous injection [5,6]. Thus, the combined treatments consisted of low-intensity US irradiation and anti-tumor agents demonstrated the significant inhibition of the tumor growth in vivo, in comparison to either anti-tumor agents used alone or US irradiation alone, thus suggesting an accelerated (booster, or synergistic) effect of US for these agents. The possible mechanism of these combination therapies using a low-intensity US might be by chiefly the first mechanism (sonoporation) described above. In addition, direct cellular damage including a vascular effect by US irradiation, anti-apoptotic effect for tumor cells, and increased free radicals (the second mechanism) might be added because of the evidence of wide areas of coagulative necrosis in irradiated tissue specimens. Furthermore, the most studies showed that no side effect was observed in any mice in the combined treatment using low-intensity US and anti-angiogenic agents, suggesting the

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safety of this new therapeutic approach compared to high intensity US therapy (HIFU), or radiotherapy currently used [5,6]. However, the mechanisms of these anti-tumor and anti-angiogenic therapy combined with low-intensity US for human cancers need to be more precisely elucidated.

Ultrasound has been generally used as a modality for diagnostic imaging in various clinical fields without producing any significant adverse effects. The neovascularization of tumors could be displayed by color Doppler US in various human solid tumors. The changes in intratumoral vascularity in xenotransplanted tumors treated by anti-angiogenesis can be demonstrated by color Doppler US in real-time with microbubble contrast agents [5,6]. Recent clinical reports using color Doppler US with a microbubble contrast agent were shown to enhance the vascularity of solid tumors, even in small lesions. The outcome of anti-cancer treatment thus could be efficiently evaluated by contrast color Doppler US. The immunohistochemical studies supported the findings of sonographic vascular density, suggesting the usefulness of contrast color Doppler to assess angiogenesis without an immunohistochemical examination in vivo. Moreover, another study additionally reported that the color Doppler vascularity index is a better indicator of tumor behavior in colon cancer patients.

It may be very useful to assess the effect of ultrasound therapy for solid tumors by contrast color Doppler US, non-invasively in real time.

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