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# The promise of sonodynamic therapy: Using ultrasonic irradiation and chemotherapeutic agents as a treatment modality

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Sonodynamic therapy (SDT) is showing promise as a potentially vital alternative to traditional cancer treatment modalities. SDT is a form of ultrasound therapy in which chemotherapeutic agents known as sonosensitizers are administered to increase the efficacy of ultrasound's preferential damage on neoplastic cells (Trendowski., 2014). The attractive features of SDT emerges from the ability to focus ultrasound energy on malignancy sites buried deep in tissues and to locally activate a preloaded sonosensitizer (Rosenthal, Sostaric, Riesz., 2004; Kuroki et al., 2007). Furthermore, SDT has shown to induce cell damage in many cancer types and appears to be a versatile treatment method (Bai W, Shen E, Hu B., 2012; Kuroki et al., 2007). It has even been shown that SDT can illicit an immune response as observed in a substantial variety of in vivo studies. Evidence of this remarkable mechanism include transient increases in infiltration of non-T regulatory (non-Treg) tumor infiltrating lymphocytes (TILs), continual infiltration of CD8+ cytotoxic T-lymphocytes (CTL) and an observable macrophage response due to cell lysis (Hu et al., 2007; Liu et al., 2012; Wu., 2013; Wu et al. 2007).

Perhaps one of the most intriguing capabilities of ultrasound is its ability to preferentially lyse cells based on size (Miller, Luque, Battaglia, Mazza, Everbach., 2003). This known fact invariably gives rise to the idea of grossly enlarging tumor cells to increase their already noticeable size difference with normal cells. Cytochalasin B is a known pharmacological agent that disrupts the actin cytoskeleton and inhibits cytokinesis by interfering with formation of the contractile ring as well as the development of the cleavage furrow (Trendowski., 2014). Consequently, the cell does not divide and an immature actin cytoskeleton remains. However, the cell continues to form nuclei and eventually becomes grossly enlarged and multinucleated. Such cells invariably have more DNA targets, increasing the likelihood of apoptosis. Furthermore, the multinucleated cells have a large cell volume, making them more susceptible for direct cell destruction. Preferential damage of malignant cells is actually easily attainable as normal cells exposed to cytochalasin B exit the cell cycle and enter a resting state until sufficient actin levels are restored. Therefore, only malignant cells that have lost the ability to enter the rest phase will become grossly enlarged and multinucleated, providing an ideal target for ultrasonic irradiation.

Work from our lab has indicated that cytochalasin B does indeed only damage leukemia cells, leaving normal blood cells, unaffected (Trendowski., 2014). The designated cell line has been promyleocytic leukemia U937 cells as they are a frequent choice for in vitro studies. The U937 cells have routinely become grossly enlarged and multinucleated, providing an ideal target based on size. The typical erythrocyte is 6-8μm, while leukocytes fair slightly better with a range of 10-15μm and an average of 12μm. By contrast, work from our lab has shown that cytochalasin B treated leukemia cells easily grow in excess of 20μm with some reaching 40μm in diameter after enough exposure(Trendowski et al., 2014). Such cells have reduced cytoskeletal integrity and are easy targets for ultrasonic irradiation. Furthermore, cytochalasin B treated leukemia cells are substantially multinucleated as cytokinesis is inhibited. This provides plenty of targets for a nucleic acid directed agent such as cisplatin or doxorubicin to attack.

The proposed therapeutic approach could provide for a potent clinical method to treat leukemias and other hematological malignancies. Ultrasound can be directed towards any area of the body, allowing for search and destroy methods to be created in which there is no place for malignant cells to hide. Preferential damage should be substantially increased when a cytochalasin B-nucleic acid agent drug cocktail is applied to ultrasonic irradiation as leukemia cells will be most affected by the treatment. SDT has even been shown to reverse drug resistance in K562/A02 leukemia cells when doxorubicin, another nucleic acid agent is combined with ultrasound (Meng, Chen, Wu, Shao, Gao, Zhao., 2008). Such results are promising and further substantiate SDT as a viable treatment modality. By using cytochalasin B and a nucleic acid agent as sonosensitizers, I propose that ultrasonic irradiation will significantly cripple leukemia cell populations, creating a basis to promote the therapeutic approach for in vivo and eventual clinical studies.

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