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## Particle Beam may have Higher Effectiveness in Treating Chemo-resistant Cancers than Low-LET Photon Beam Therapy

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### Editorial

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It is now well-established that outcomes of radiotherapy depend on quality of radiation. A large body of experimental evidences suggests that high-LET (linear energy transfer) radiation or particle radiation has the ability to kill tumor cells more efficiently than low-LET photon beams such as X-rays and  $\gamma$ -rays<sup>[1,2]</sup>. The unique characteristics of particle beam, which includes precise dose distribution, formation of complex and "clustered" DNA damage in target cells, capacity to kill cells with equal effectiveness irrespective of their cell cycle stage and oxygen content, ability to cause biological damage by direct action, and inverse dose-depth relation are considered to be responsible for higher relative biological effectiveness (RBE) than low-LET photon beams. However, the efficacy of particle radiation in killing chemo-resistant cells compared to low-LET radiation is not well-documented.

Despite the current success of chemotherapy in treating various cancers, drug resistance is the major factor that restricts the effectiveness of chemotherapy. Some of the tumors are intrinsically resistant to chemotherapeutic drugs, while other tumors may acquire drug resistance during treatment, after showing initial sensitivity to chemotherapy. Acquired resistance to chemotherapeutic agents is a complex process and involves various mechanisms that includes ABC transporter- and MDR proteins-mediated active efflux of chemotherapeutics, modification of drug targets, disruption of mitotic check points in cancer cells promoting uncontrolled cell growth, acquiring the ability to detoxify drugs and/or enhanced ability of DNA repair<sup>[3]</sup>. Therefore, strategies to overcome chemo-resistance are urgently needed.

Methotrexate (MTX) is a folate antagonist and is used in treating various cancers, because of its ability to block DNA synthesis in cells with high proliferative capacity. MTX halts DNA synthesis by inhibiting the enzyme dihydrofolate reductase (DHFR). However, long term administration of MTX to patients often results in emergence of drug resistance. Previously, to elucidate the molecular mechanisms underlying MTX-resistance, an in vitro model system was developed by exposing Chinese hamster lung fibroblast (V79) cells to UV radiation followed by incremental sequential dose of MTX and the MTX-resistant cell was designated as M5<sup>[4]</sup>. M5 cells were found to be resistant to  $\gamma$ -rays, H<sub>2</sub>O<sub>2</sub> and other chemotherapeutic drugs than its counterpart V79<sup>[4,5]</sup>. Although, the exact mechanisms of radiation resistant is not completely understood, gene expression studies reveal that anti-apoptotic and pro-survival genes, like dhfr, hmsh3 (hamster homologue of human mismatch repair), mt-nd1 (mitochondrially encoded NADH dehydrogenase 1), mt-nd4 (mitochondrially encoded NADH dehydrogenase 4) and bcl2 (B-cell lymphoma 2) are over-expressed in M5 cells, which may contribute to make this M5 cells resistant to  $\gamma$ -rays<sup>[6,7]</sup>.

Pathak et al. (2007a and 2007b) showed that different particle radiations can kill M5 cells more effectively than low-LET  $\gamma$ -rays<sup>[8,9]</sup>. At 37% survival (D<sub>37</sub>), the RBE values for M5 cells exposed to <sup>7</sup>Li beam (LET=60 keV/ $\mu$ m) and <sup>12</sup>C beam

(LET=295 keV/ $\mu\text{m}$ ) were 4.39 and 2.58, respectively, relative to  $^{60}\text{Co}$   $\gamma$ -rays [8,9]. This higher potency of particle radiation to kill drug-resistant cell was found to be strongly correlated with micronuclei formation, chromosome aberration induction and cellular apoptosis [8,9]. Moreover, particle radiations-induced survival curves for M5 cells were linear in nature suggesting damaged produced by particle radiation in MTX-resistant cells is irreparable, while  $\gamma$ -irradiation induced linear-quadratic survival curves for the same chemo-resistant cells indicating damages at lower dose regions can be repaired [8,9]. Similar higher radiation sensitivity was observed in paclitaxel-resistant human H460 and A549 cell lines when exposed to proton beam in comparison to low-LET photon irradiation [10]. Proton beam-mediated higher radiation sensitivity in drug resistant cells was found to be related with higher expression of coxsackievirus and adenovirus receptor (CAR), a marker for cancer stem cell, and  $\beta$ -catenin [10]. These findings are promising for the development of novel treatment regimen using particle beam in treating cancer patients who has developed resistance to chemotherapeutic drug.

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## CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

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