Treating cancer with an iron fist

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Cancer cells have a greater demand for iron compared to normal cells, mostly to meed demands for increased metabolism. It has been known for decades that cancer cells tend to up-regulate their iron uptake. More recently, it was discovered that the cancer cells also down-regulate the iron efflux by decreasing expression of ferroportin (FPN), thereby increasing iron retention. Importantly, FPN levels have also been negatively correlated with patient prognosis. This metabolic shift in cancer cells to a higher baseline iron content alo represents a therapeutic opportunity as cancer cells are potentially more vulnerable than non-cancer cells . We have found that ferumoxytol (Feraheme; FH), an FDA-approved iron oxide nanoparticle for iron deficiency treatment, can be used as a drug carrier, delivering payload of even several drugs to solid tumors, but also as an anti-cancer therapy alone. Using leukemia cell lines and primary acute myeloid leukemia patient samples (PDX), we show that low expression of FPN in the leukemic cells is a key signature. Reactive oxygen species produced by free ferrous iron lead to increased oxidative stress and cell death. Ferumoxytol treatment results in a significant reduction of disease burden in a murine acute myeloid leukemia (AML) model and patient-derived xenotransplants bearing leukemia cells with low ferroportin expression. Our findings show how a clinical nanoparticle previously considered largely biologically inert could be rapidly incorporated into clinical trials for patients with leukemia with low ferroportin levels. Importantly, we can radiolabel the nanoparticles for imaging and also load additional drugs into them. As AML leads to liver and spleen disease burden, we sought to radiolabel FH to track liver and spleen size by PET as well as assess the therapeutic benefits of FH in AML. We employed chelator free labeled ^{89}Zr-FH to image liver and spleen size in mice as well as track ^{89}Zr-FH distribution outside of these key organs. We found that mice administered ^{89}Zr-FH had an increased mean survival to saline controls and mice that died first had larger spleen sizes, presumably from disease burden. Therapy of tumors with iron oxide nanoparticles can in the right biological setting open an avenue for an entire new therapy approach, termed oxidative ferrotherapy, probably playing into ferroptosis mechanisms. Furthermore, efforts are underway to elucidate the role of nanoparticles in the tumor environment more closely.