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Role of chloroquine as an anticancer agent

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ABSTRACT

Chloroquine is a prototype antimalarial drug used to prevent and treat malaria, amebiasis and other autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus. The drug acts as an autophagy inhibitor where autophagy is a self-destructive process which is needed to balance sources of energy at developmental process and in response to nutrient deprivation. New studies have shown the crucial role of chloroquine in cancer treatment and is been extensively used as a monotherapy or adjunct therapy in various types of cancer. This review summarizes the role of chloroquine and its action as an autophagy inhibitor in cancer treatment and also the various safety issues concerning with the same.



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INTRODUCTION

Chloroquine is a quinolone derivative which is used to treat malaria. It exerts its action by inhibiting the heme polymerase activity which in turn leads to the increase of free heme. This has lethal effects for the parasite and disrupts its membrane function. It may also interfere with the biogenesis of nucleic acids within the parasite. It is extensively used in the treatment of all types of malaria except for those caused by chloroquine resistant *Plasmodium falciparum*. This drug also has potential anticancer properties when given as a monotherapy or as an adjuvant therapy with other anticancer agents for the treatment of various types of cancer. Chloroquine is an autophagy inhibitor and hence used as a novel anticancer drug. Its action in inhib-

iting lysosomal protease leads to autophagy blockade and further preventing autophagosome-lysosome fusion events have made a greater acceptance as an autophagy inhibitor in vitro and in vivo (Amaravadi *et al.*, 2011).

Autophagy

Autophagy is defined as a group of mechanisms involved in the regulation of cell and tissue homeostasis. It has a major role in many physiological functions such as development, differentiation, normal growth and immunity.

It is an intercellular degradation system which is required to balance energy during phases of development and also in response to nutrient stress. It also degrades damaged or unwanted proteins and cellular organelles. Cancer cells are thought to use autophagy as a source of energy in the unfavorable metastatic environment. This mechanism enables cancer cells to use autophagy as a source of energy in unfavorable conditions.

Chloroquine helps tumor cells to overcome stressors in the tumor microenvironment and also the injuries caused due to endocrine therapy, chemotherapy and radiation therapy. Therefore, it functions as a cell-survival pathway. It also supports the progression and metastatic dissemination of established tumors (Manic *et al.*, 2014). Since the cancellation of autophagy via knockdown of

autophagy-related molecules promotes the re-sensitization of therapy-resistant cancer cells to traditional cancer therapies, development of clinically relevant autophagy inhibitors has been widely accepted.

Chloroquine as an autophagy inhibitor

Chloroquine, a widely used antimalarial agent and a weak base demonstrated with good safety profile (Lee *et al.*, 2011), gets protonated in acidic compartments like late endosomes and lysosomes. Chloroquine undergoes fusion events by alkalinizing these acidic compartments thus resulting in blockade of the basal and stimulated autophagic flux (Maes *et al.*, 2013).

Inhibiting the lysosomal activity of the autolysosome by arresting the degradation results in the failure of energy supply through the autophagy pathway. Since autophagy promotes cancer, it may expose cancer cells through inhibiting autophagy. The normal dose ranges between 100 – 500 mg/day. At low doses side effects are usually minimal but many toxic effects occur at high doses such as visual disturbances, gastric problems, electrocardiogram changes, headaches and pruritus.

Chloroquine also promotes vessel normalization wherein it reduces the tumor hypoxia by improving the structural and functional features of the tumor blood vessels (Carmeliet *et al.*, 2011). The presence of dysfunctional and disorganized tumor vessels is a characteristic feature of many aggressive cancers and favours the hostile tumor micro-environment which is characterized by acidosis, hypoxia, and high interstitial fluid pressure, while reducing antitumor immune responses and the efficacy of anticancer treatments (Carmeliet *et al.*, 2011).

Chloroquine effects on tumor vasculature

New studies have linked the impact of chloroquine in tumor stromal cells and carcinogenesis. Studies reveal that chloroquine improves the structural and functional features of the tumor blood vessels through vessel normalization mainly by reducing tumor hypoxia (Carmeliet *et al.*, 2011).

The blood vessels that are permeable, facilitates invasiveness and tumor propagation. The drug reduces vessel density and tortuosity and improves endothelial cell arrangement and tight junction formation. It also reduces tumor vessel leakiness and increases tumor vessel perfusion. Importantly, tumor vessel normalization in response to chloroquine also enhances the delivery and efficacy of chemotherapeutic agents (Dobrowolski *et al.*, 2012).

When autophagy gets compromised in melanoma cells primary tumor growth and its metastasis is

reduced. This also fails to normalize tumor structure or prevention from further intravasation. These autophagy compromised cancer cells have reduced survival capacity in the blood stream and therefore they lack the metastatic potential. This confirmed that blocking cancer cell-autonomous autophagy constrains metastatic propagation following tumor cell intravasation rather than preventing it. Chloroquine effect of tumor vessel normalization is triggered independent of autophagy in the cancer cells or in endothelial cells.

Emerging role in cancer treatment

Studies have shown that chloroquine could preferentially penetrate human malignant cells and enhances the radiation response of cultured tumor cells. The enhancement efficacy is due to the impairment of post-radiation recovery process. Studies also confirm that chloroquine could effectively sensitize multi-drug resistance tumor cells in response to certain anti-neoplastic drugs such as vincristine (Inba and Malayama 1988).

In a study conducted in mice with breast tumors have suggested that chloroquine when combined with other chemotherapeutic agents, stimulates immunogenic tumor cell death. The study stated that chloroquine when given after radiation increases the rapid cell death of MCAK (Mitotic Centromere-associated Kinesin) breast cancer cells *in vitro* and that cells are immunogenic and can enhance radiation induced tumor regression *in vivo* (Ratikan *et al.*, 2013).

Chloroquine action as an antiautophagy inhibitor has also made it useful in the treatment of other cancers such as pancreatic adenocarcinoma, prostate cancer, renal cell carcinoma and ovarian cancer (Mirzoeva *et al.*, 2011; Li *et al.*, 2013; Zhang *et al.*, 2012).

Chloroquine effect in other organs

Autophagy is also used by normal cells to maintain intracellular homeostasis. It is necessary for the stimulation of innate and adaptive immune responses. Therefore, inhibition of autophagy not only exposes cancer cells but also normal organs to chemotherapy (Rabinowitz *et al.*, 2010; Sasaki *et al.*, 2010) and also increases the risk to develop other diseases such as infective diseases, neurodegenerative conditions (Ma *et al.*, 2013). It also promotes some degree of immunosuppression.

Chemotherapy being a hallmark in the treatment of various types of cancer causes acute to chronic organ toxicities. The combined use of chloroquine with chemotherapeutic agents may exacerbate injuries to vital organs due to autophagy deficiency.

Table 1: Role of chloroquine in various types of cancers

Cancer type	Effect	Mechanism
Non small cell lung cancer	Synergistic effect with lindamycin	Chloroquine enhances lidamycin induced apoptosis of non small cell lung cancer via a Bax-related, caspase-dependent, P53-independent pathway and inhibits its autophagy (Fang <i>et al.</i> , 2014).
Colorectal cancer	Enhanced 5-fluorouracil effect on colorectal cancer	Chloroquine amplify 5-fluorouracil induced inhibition of tumor growth in-vitro and in-vivo. Mitogen-activated protein kinase 14 (MAPK14)/p38 α is involved in colon cancer cell resistance to 5-fluorouracil and irinotecan (Sui <i>et al.</i> , 2013; de la Cruz-Morcillo <i>et al.</i> , 2012).
Esophageal cancer	Improved effects of chemotherapeutic drugs	Improve the efficacy of chemotherapeutic agents such as cisplatin and 5-fluorouracil (de la Cruz-Morcillo <i>et al.</i> , 2012; Liu <i>et al.</i> , 2011).
Glioblastoma	Enhanced bevacizumab efficacy	Bevacizumab, which is used to treat glioblastoma has shown treatment failure due to resistance to malignant cell clones. When combined with chloroquine, tumor growth is disrupted and overcomes resistance to antiangiogenic therapy for glioblastoma.
Breast cancer	Inhibits autophagy induction by epirubicin; enhanced effect of tumor cell killing as well as independent effect in sensitizing the tumor cells (de la Cruz-Morcillo <i>et al.</i> , 2012).	Epirubicin induce autophagy in human breast cancer MCF-7 cells leading to MCF-7 cells protection from epirubicin induced apoptosis (Sun <i>et al.</i> , 2011). Autophagy also produce antiestrogen resistance and autophagosome blocking, significantly reducing the emergence of antiestrogen resistant breast cancer cells (Schoenlein <i>et al.</i> , 2009; Wilson <i>et al.</i> , 2011).
Leukemia and mantle cell lymphoma	Enhanced treatment outcomes	Decreases cell viability of B-chronic lymphocytic leukemia in a dose dependent manner (Lagneaux <i>et al.</i> , 2001).
Hepatocellular carcinoma	Improved effect of bevacizumab	Inhibition of growth of hepatocellular carcinoma (de la Cruz-Morcillo <i>et al.</i> , 2012; Ding <i>et al.</i> , 2011).

The kidneys are mainly affected compared to other organs as it's been the fundamental organ in excretion and many metabolites of chemotherapeutic drugs are excreted via kidney tubular epithelial cells (de Jong *et al.*, 2006).

Drugs used as chemotherapy causes harm to kidneys by damaging the proximal tubules. Cisplatin, a commonly used chemotherapeutic agent cause kidney damage such as DNA damage, mitochondrial damage, oxidative stress, ischemic injury caused by vascular damage, through several mechanisms (Pabla *et al.*, 2008). A recent study showed the protective role of autophagy against cisplatin induced renal injury (Takahashi *et al.*, 2012). The study pointed out firstly that autophagy protects proximal tubular cells from mitochondrial oxidative stress (the clearance of mitochondria by autophagy is specifically called 'mitophagy'). Secondly, autophagy also protects proximal tubular cells from DNA damage and thirdly, autophagy protects proximal tubular cells from abnormal protein accumulation.

In addition, autophagy also protects proximal tubular cells from ischemic injury (Kimura *et al.*, 2011). Thus, via autophagy inhibition, chloroquine may cause chemotherapy-induced kidney injury through multiple pathways.

Other organs are also affected apart from kidneys. This includes brain, liver, heart and hematopoietic cells (Komatsu *et al.*, 2005). Bone marrow depression caused by chemotherapies is worsened by the addition of chloroquine. Certain antibiotics such as doxorubicin and daunorubicin can cause cardiotoxicity in a dose dependent manner probably through DNA damage, and the addition of chloroquine to the therapeutic regimen could worsen cardiotoxicity.

CONCLUSION

Accumulating evidence imply that chloroquine is a potent antimalarial drug which can be used in various cancer treatment and to potentiate the efficacy of chemotherapeutic agents by acting as an autophagy agent as well as acting on the tumor

vasculature. Chloroquine exposes cancer cells to chemotherapy and exerts anticancer effects through inhibiting autophagy. On the other hand, the very effect of chloroquine to inhibit autophagy could also expose normal cells, leading to acute to chronic organ toxicity which emphasize on the importance of implementing the therapy with caution.

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