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Repurposing Antimalarial Drug Mefloquine for Cancer Treatment

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Abstract

Mefloquine (MQ) is a quinoline class of drugs that has been in clinical use for the last four decades for the prophylaxis and treatment of malaria. Several recent literature studies on MQ illustrate that this drug exhibits good to excellent cytotoxicity and cell proliferation inhibition against several cancer cells. MQ also exhibits good *in vivo* tumor growth inhibition as a single agent and effectively synergizes with primary cancer chemotherapeutics in arresting tumor growth. Mechanism of action studies indicate that MQ has pleiotropic effects on cancer cells that include inhibition of autophagy, lysosomal disruption, inhibition of various signaling pathways, and inhibition of Pgp pumps. Based on the *in vitro* and *in vivo* anticancer efficacy data, MQ has excellent potential to succeed as an adjuvant therapy as well as a primary agent in combination with chemotherapeutics for many solid and hematological malignancies. MQs ready and inexpensive availability and long-standing record of clinical use qualify this drug for repurposing for anticancer applications.

Keywords: Mefloquine; AMPK; Oxidative stress; Drug-efflux pumps; Lysosomotropic; Autophagy; Drug repurposing; Anti-cancer therapy; PI3K/AKT/mTOR

Introduction

Introduction of chemotherapy in conjunction with surgery and radiation therapy for cancer treatment has increased the long-term survival rate for a wide range of cancers. However, many patients treated with chemotherapy often relapse and become drug resistant leading to patient mortality. Cancer chemotherapy is also associated with numerous life-threatening side effects including severe myelosuppression and reduced immune function, infertility, and neuro, nephro, and cardio-toxicities. Hence, novel therapeutic agents that have minimal side effects and that preferably work on drug-resistant patients are urgently required for cancer treatment. The repurposing of existing clinically approved drugs for new indications has become an important process for treating various diseases [1-6]. If successful, it can dramatically decrease the time, cost, and steps involved in the drug discovery process. Since long-term safety data in clinical practice are already available for these drugs, human trials can be initiated very quickly for new applications. There have been several studies in the recent past to reposition the existing non-cancer drugs for cancer treatment due to the burgeoning costs in drug development, consequent high treatment costs, and their limited success in improving overall survival rate [1-6]. This review summarizes the potential of developing the antimalarial drug mefloquine for broad-spectrum cancer treatment.

Mefloquine (MQ) is a quinoline class of antimalarial agents used for chemoprophylaxis and the treatment of malaria (Figure 1) [7,8]. MQ has two chiral centers and can exist in two diastereomeric forms. However, it is clinically used as an enantiomeric mixture of the erythro isomer. MQ has been in clinical usage for malaria for more than three decades. It is readily available, inexpensive, and is on the World Health Organization's list of essential medicines. Despite its clinical use for decades, the precise mechanism of action of MQ was not determined until recently; Wong et al. determined the mechanism of action of MQ and found that it inhibits protein synthesis by targeting the GTPase-associated center in the 80S ribosome of Plasmodium falciparum [9].

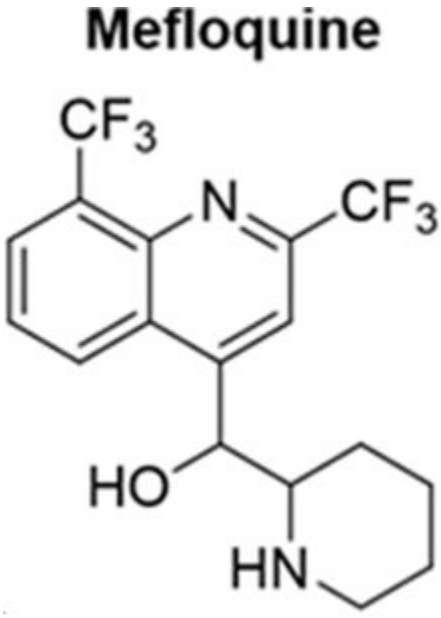

Figure 1: Chemical structure of mefloquine.

The quinoline class of antimalarial agents, including chloroquine, have been studied as lysosomotropic agents and autophagy inhibitors for cancer treatment [10-15]. However, their lack of potency limits

their use as anticancer agents. Recent studies indicate that quinoline antimalarial agent MQ is more potent than chloroquine and primaquine across several cancer cell lines and has prompted several investigators to explore the potential of MQ for cancer treatment [16-33]. This review summarizes some of the studies that have been recently carried out on various cancers to elucidate the cellular and molecular mechanisms of action of MQ.

MQ disrupts lysosomal integrity

Oncogenesis involves numerous changes to lysosomes and their function that include elevated lysosomal biogenesis, increased hydrolase activity, alterations to the lysosomal membrane, and heightened secretion of lysosomal contents to the extracellular space. Such lysosomal modifications result in cancer recurrence and aggressive proliferation, and elevated intratumoral activity of lysosomes often leads to poor prognosis. Several literature reports also indicate the presence of extracellular lysosomal enzymes in promoting cancer invasiveness, angiogenesis and progression. Hence, lysosomes have become an important molecular target in cancer therapy [14,15]. In this regard, disruption of lysosomal integrity has been implicated as one of the molecular mechanisms of action of MQ in various cancer cells.

In vitro and *in vivo* effects of MQ on acute and chronic myelogenous leukemia (AML and CML)

Sukhai et al. have shown that MQ exhibited selective toxicity for primary AML cells and AML progenitor cells compared to normal hematopoietic cells and hematopoietic progenitor cells [16]. MQ also had selective effect on clonogenic growth of AML cells. *In vivo* anticancer efficacy studies with mouse lymphoma cells MDAY-D2, human AML cell line OCI-AML2, and human chronic myelogenous leukemia K562 were carried out to evaluate the potential of MQ towards leukemia treatment [16]. These studies revealed that MQ-treated groups exhibited significant tumor growth inhibition as single agents compared to vehicle-treated groups. Mechanism of action studies revealed that MQ disturbed lysosomes, permeabilized lysosome membranes, and released cathepsins into cytosol [16].

Xiang et al. showed that MQ induced apoptosis in CML cells and blast-phase CML CD-34+ progenitor cells in a dose-dependent manner [17]. MQ also inhibited colony formation and self-renewal capacity of tyrosine kinase inhibitor (TKI) resistant BP-CML CD-34+ cells. Significantly, MQ exhibited excellent synergy with TKIs imatinib and dasatinib. Mechanism of action studies indicated that MQ induced oxidative stress via upregulation of mitochondrial superoxidase and disrupted lysosomal integrity and function in CML cells [17].

In vitro studies of MQ against glioblastoma multiforme (GBM)

Geng et al. reported potent inhibition of the cell viability of GBM cell line U87 by MQ with IC50 values at 10 μM range [18]. MQ also inhibited cell proliferation of other GBM cells LN308, U251, and LN229. Although the exact mechanism of action of MQ was not determined on these cell lines, it was reasoned to induce antiproliferative effects through lysosomal disruption based on the studied mechanism of chloroquine [18].

The above studies indicate that MQ exhibits selective cytotoxicity against AML, CML, and GBM cells and the general mechanism of action includes disruption of lysosomal integrity and release of several lysosomal proteins into the cytosol. These studies also highlight the importance of lysosomal function in cancer cell proliferation, and perturbations may lead to therapeutic efficacy.

MQ inhibits autophagy in cancer cells

Autophagy is a critical biological process and plays an important role in the recycling of intracellular proteins and organelles. This helps in the prevention of accumulation of cytotoxic waste products and provide biosynthetic building blocks under nutrient deprived conditions [19]. Autophagy is highly upregulated in numerous cancer cells and acts as a survival mechanism in support of rapid cell turnover. Inhibition of autophagy has been shown to improve the therapeutic efficacy in cancer treatment [20]. In this regard, MQ has been studied as an autophagy inhibiting agent against various breast cancer (BCa) cells by Sharma et al. [21].

In this study, MQ was tested against hormone positive BCa cells MCF7, T47D, and triple negative BCa cells MDA-MB-231 and MDA-MB-468. MQ exhibited excellent cell proliferation inhibition and induced apoptosis in the tested cell lines at low micromolar concentrations indicating the importance of its activity against hormone positive and negative BCa cells. Significantly, MQ increased chemosensitivity of BCa drug paclitaxel against T47D and MDA-MB-231 cells. Remarkably, MQ was also effective against doxorubicin-resistant MCF7-DoxR cells at low micromolar concentrations [21]. Detailed mechanisms of action of MQ against BCa cells were carried out, and these studies indicated that MQ inhibited autophagy by upregulating LC3 expression, conversion of LC3-I to LC3-II and autophagy inhibition at the stage of autophagosome formation. Further mechanistic studies revealed that MQ triggered ER stress in BCa cells. However, ER stress was only induced at high concentrations of MQ and was not responsible for MQ's cytotoxic effects [21].

The above study reveals that MQ inhibits autophagy at the stage of autophagosome formation in hormone positive and triple negative BCa cells. This study also highlights the importance of autophagy inhibition in eliciting anti-cancer effects and illustrates the pleiotropic effects of MQ.

MQ perturbs cancer cell signaling pathways

Malignant transformation often results in the disruption of cell signaling pathways that play an important role in providing hallmark characteristics of cancer. Survival, proliferation, and motility are tightly controlled by numerous pathways, and therapeutic targeting of aberrant signaling pathways has become an important target for cancer drug development [22,23]. In this regard, MQ has been studied for therapeutic targeting of several cell signaling pathways.

In vitro and *in vivo* studies of MQ in prostate cancer

Yan et al. utilized MQ for prostate cancer treatment [24]. They utilized two human prostate cancer cell lines DU145 and PC3 originated from brain and bone metastasis respectively. Treatment with MQ induced cytotoxicity with an IC50 of ~10 μM for both cell lines. Increasing the concentration up to 20 μM completely abolished the cell proliferation. Interestingly, MQ did not exhibit any cytotoxicity at 10 μM against human foreskin fibroblast Hs68, indicating its selectivity towards cancer cells [24]. *In vivo* efficacy studies were carried out in a mouse PC3 model. The MQ treated group exhibited increased lifespan and 75% of the mice survived up to 47 days and 50% of the mice survived up to 51 days. In contrast, only 25% of the mice in the control

group survived up to 47 days indicating the survival advantage of the mice treated with MQ [24]. Mechanism of action studies indicated that MQ caused hyperpolarization of mitochondrial membrane potential and increased generation of ROS resulting in rapid cancer cell death. Further studies indicated that MQ-mediated ROS inhibited Akt phosphorylation and activated JNK, ERK and AMPK signaling [25].

In vitro and *in vivo* studies of MQ in gastric cancer

Liu et al. studied the potential of MQ against gastric cancer [26]. This study revealed that MQ potently inhibited cell proliferation and induced apoptosis against several human gastric cancer cell lines with IC50 values ranging from 0.5-0.7 μM. Further translation of these studies was carried out in two gastric carcinoma *in vivo* models with YCC1 and SNU-1 cells. In the case of YCC1, MQ and paclitaxel exhibited moderate tumor growth inhibition as single agents, but their combination completely suppressed tumor growth and by the end of the three-week treatment period, the tumor volume was found to be less than the initial point indicating regression of the tumors [26]. In the case of SNU-1, MQ again exhibited moderate tumor growth inhibition, but the combination with paclitaxel arrested the tumor growth significantly. Mechanism of action studies indicated that MQ inhibitory effects were mainly attributed to the inhibition of PI3K/Akt/mTOR signaling pathway. At IC50 concentrations MQ did not affect levels of ROS generation, but at higher concentrations it slightly increased ROS but the observed cell proliferation inhibition was not attributed to ROS generation in gastric cancer cells [26].

In vitro and *in vivo* studies of MQ in cervical cancer

Li et al. showed the therapeutic benefits of MQ against cervical cancer [27]. This study indicated that MQ inhibited cell proliferation, anchorage-independent colony formation, and induced apoptosis in cervical cancer cell lines HeLa, SiHa, and C-33A. *In vivo* efficacy studies were carried out using HeLa derived tumor xenografts. It was found that the combination of MQ and paclitaxel exhibited significant tumor growth inhibition thus highlighting the importance of MQ for cervical cancer treatment [27]. Mechanism of action studies indicated that MQ caused mitochondrial dysfunction by decreasing membrane potential, decreasing ATP generation, and increasing ROS generation. Further studies showed that MQ also inhibited the activation of mTOR signaling pathway in HeLa cells [27].

The above *in vitro* and *in vivo* studies on prostate, gastric, and cervical cancers indicate that MQ exhibits excellent activity and its anticancer effects are attributed to ROS generation and inhibition of signaling pathways. These studies also expand on the pleiotropic mechanisms of MQ against various cancer cells and illustrates potential utility as a broad-spectrum anticancer agent.

MQ inhibits drug efflux pumps

Cancer cells overexpress MDR proteins such as P-glycoprotein (Pgp) or MDR-associated proteins (MRP) and they lead to an increased efflux of a drug, decreased uptake, evading apoptosis, and consequent drug resistance [28,29]. This is a significant clinical problem as many patients initially respond to standard treatment but eventually become drug resistant. Hence, and efficient chemosensitization of drug resistant cancer cells expands the utility of currently used anticancer agents. In this regard, MQ has been investigated as an inhibitor of drug efflux pumps and chemosensitization of drug resistant cancer cells.

Kim et al. found that MQ as a single agent exhibited similar biologic activity for drug-sensitive KB cells and drug-resistant KBV20C cancer cells [30]. MQ in combination with antimitotic agent vinblastine was found to highly sensitize KBV20C cancer cells. Interestingly, co-treatment of MQ with vinblastine did not inhibit the viability of drug sensitive KB cells. Mechanism of action studies indicated that MQ potently inhibited Pgp in a dose and time-dependent manner [30].

Riffkin et al. reported that MQ potently inhibited MDR1 Pgp and its functional activity [31]. This resulted in an increase in sensitivity of vinblastine to its resistant cell CEM/VBL100. In the absence of MQ, CEM/VBL100 cells were resistant to vinblastine up to 160 nM concentration. But in the presence of 8 μM MQ, vinblastine inhibited the cell growth at ~3 nM concentration illustrating MQ's ability to sensitize drug resistant cells for chemotherapy [31].

Fujita et al. reported the MQ-induced sensitization of chemotherapeutic agent doxorubicin in resistant CML cell line K562-DoxR [32]. MQ potentiated the cytotoxicity of doxorubicin in K562-DoxR cells at a concentration of 0.5-3 μM. Interestingly, MQ did not exhibit any synergistic activity on the drug-sensitive parent cell line K562. Mechanism of action studies indicated that MQ inhibited Pgp activity and also reduced the expression of Pgp in K562-DoxR cells [32].

The above studies indicate that MQ potently inhibits drug efflux pumps that are often upregulated in drug resistant cancer cells. By inhibiting these pumps, MQ chemo-sensitized resistant cells to standard chemotherapeutic agents. Since drug resistance to chemotherapy is a significant clinical problem, utilization of MQ along with standard therapies should lead to a better therapeutic outcome.

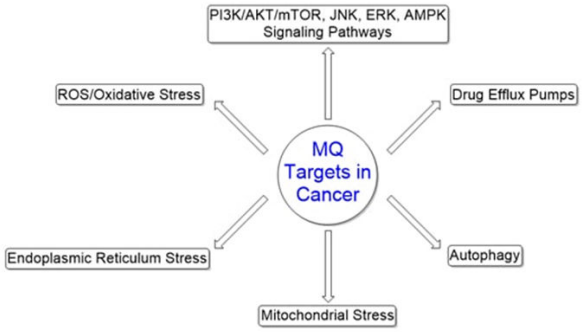

Figure 2: MQ targets in various cancer cells.

Conclusion

In conclusion, it is clear from several literature reports cited above that MQ exhibits potent cytotoxic and cell proliferation inhibition properties against many solid and hematological malignancies. The IC50 values are in the sub-micromolar to low micromolar range indicating its superiority over other quinoline class antimalarial agents chloroquine, hydroxychloroquine, and primaquine which typically require high micromolar concentrations to elicit anticancer effects. MQ's *in vitro* results have been substantiated with excellent *in vivo* studies that highlight MQ's potential as a single agent and also in combination with primary chemotherapeutics. It has been especially found to sensitize various drug-resistant cancer cells providing opportunities for patients who have undergone primary chemotherapy

and also patients who have become drug resistant. The mechanism of action studies indicate that MQ exhibits pleiotropic effects including inhibition of autophagy, lysosomal disruption, inhibition of various signaling pathways, and inhibition of Pgp pumps in several cancer cells (Figure 2). Although long-term usage of MQ has psychiatric and neurological side effects in some patients, its utility may be justified in late-stage cancer patients with limited treatment options. Despite the impressive *in vitro* and *in vivo* activity against a wide variety of cancers, it is surprising that only a small clinical trial of MQ is being studied in humans in combination with temozolomide, memantine, and metformin for post-radiation glioblastoma multiforme patients [33]. MQ is inexpensive and its ready availability in large scale provides impetus to explore its potential for clinical trials in countries where highly expensive and newer cancer medications are not easily accessible. This review also highlights the importance of repurposing MQ with chemo and radiation therapy to initiate clinical trials in various cancers to realize its potential as a broad-spectrum anticancer agent.

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Competing Interests

The authors declare that they have no competing interests.

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