Chloroquine and Hydroxychloroquine

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The chloroquine family of antimalarials has a long history of use, spanning many decades. Despite this extensive clinical experience, novel applications, including use in autoimmune disor-ders, infectious disease, and cancer, have only recently been identified. While short term use of chloroquine or hydroxychloroquine is safe at traditional therapeutic doses in patients without pre-disposing conditions, administration of higher doses and for longer durations are associated with toxicity, including retinotoxicity. Additional liabilities of these medications include pharmacokinetic profiles that require extended dosing to achieve therapeutic tissue concentrations. To improve chloroquine therapy, researchers have turned toward nanomedicine reformulation of chloroquine and hydroxychloroquine to increase exposure of target tissues relative to off-target tissues, thereby improving the therapeutic index.

Keywords: chloroquine ; hydroxychloroquine ; Nanoformulation ; cancer therapeutics

1. Introduction

Chloroquine (CQ) and hydroxychloroquine (HCQ) have been used for decades in the prevention and treatment of malaria and in the treatment of some autoimmune diseases such as lupus erythematosus and rheumatoid arthritis due to their immunomodulatory properties[1][2][3].

2. Effect

Despite being considered old drugs, CQ and HCQ have generated new interest due to their anticancer activity both in preclinical and clinical studies[4][5]. Researchers have shown these drugs act through a variety of antineoplastic mechanisms such as autophagy disruption, tumor vessel normalization, immunomodulation, and inhibition of metastasis, acting both directly on the tumor parenchyma and tumor microenvironment[6][7]. Chloroquines have been shown effective either as monotherapies or as adjunct therapies, sensitizing cancer cells to existing cytostatic agents as well as targeted therapies[7]. For example, HCQ has been shown to synergize with MEK pathway inhibitors for effective treatment of RAS-driven cancers, and CQ has been shown to inhibit melanoma growth through modifying tumor-associated macrophage (TAM) from the M2 immunosuppressive/pro-tumor phenotype to M1 immunostimulatory/antitumor phenotype[8][9].

CQ and HCQ have also recently received worldwide attention due to their potential use in treating coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Previous studies showed in vitro efficacy of these drugs against Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory coronavirus (SARS-CoV), and a recent study demonstrated CQ could effectively inhibit viral infection of SARS-CoV-2 in vitro[10][11][12]. As a result, scientists suggested their assessment in patients, leading to emergency use authorization for HCQ and the initiation of several clinical trials. CQ and HCQ are both basic amphiphiles that concentrate in the lysosome and inhibit lysosomal function as their primary mechanism of action[13]. While CQ and HCQ also have similar toxicity profiles and are equipotent, chloroquine is much more toxic (2-fold)[13]. Although short-term administration of either drug is generally well-tolerated, except in patients predisposed to arrhythmia, chronic dosing and high-dose regimens can cause severe side effects such as irreversible retinal toxicity[14][15][16]. CQ and HCQ have similar pharmacokinetic (PK) properties, including high volume of distribution and prolonged plasma half-lives between 40 and 50 days, which requires weeks of dosing to achieve steady-state therapeutic concentrations[17]. Reformulation of CQ and HCQ to improve their PK and safety profile may support the use of these drugs for applications such as cancer and infectious diseases.

References

1. Chew, C.Y.; Mar, A.; Nikpour, M.; Saracino, A.M. Hydroxychloroquine in dermatology: New perspectives on an old drug. Australas J. Dermatol. 2020, 61, e150–e157.

2. Mian, A.; Ibrahim, F.; Scott, D.L. A systematic review of guidelines for managing rheumatoid arthritis. BMC Rheumatol. 2019, 3, 42.
3. Taherian, E.; Rao, A.; Malemud, C.J.; Askari, A.D. The biological and clinical activity of anti-malarial drugs in autoimmune disorders. Curr. Rheumatol. Rev. 2013, 9, 45–62.
4. Dolgin, E. Anticancer autophagy inhibitors attract ‘resurgent’ interest. Nat. Rev. Drug Discov. 2019, 18, 408–410.
5. Shi, T.T.; Yu, X.X.; Yan, L.J.; Xiao, H.T. Research progress of hydroxychloroquine and autophagy inhibitors on cancer. Cancer Chemother. Pharmacol. 2017, 79, 287–294.
6. Maes, H.; Kuchnio, A.; Peric, A.; Moens, S.; Nys, K.; De Bock, K.; Quaegebeur, A.; Schoors, S.; Georgiadou, M.; Wouters, J.; et al. Tumor vessel normalization by chloroquine independent of autophagy. Cancer Cell 2014, 26, 190–206.
7. Verbaanderd, C.; Maes, H.; Schaaf, M.B.; Sukhatme, V.P.; Pantziarka, P.; Sukhatme, V.; Agostinis, P.; Bouche, G. Repurposing Drugs in Oncology (ReDO)-chloroquine and hydroxychloroquine as anti-cancer agents. Ecancermedicalscience 2017, 11, 781.
8. Chen, D.; Xie, J.; Fiskesund, R.; Dong, W.; Liang, X.; Lv, J.; Jin, X.; Liu, J.; Mo, S.; Zhang, T.; et al. Chloroquine modulates antitumor immune response by resetting tumor-associated macrophages toward M1 phenotype. Nat. Commun. 2018, 9, 873.
9. Kinsey, C.G.; Camolotto, S.A.; Boespflug, A.M.; Guillen, K.P.; Foth, M.; Truong, A.; Schuman, S.S.; Shea, J.E.; Seipp, M.T.; Yap, J.T.; et al. Protective autophagy elicited by RAF-->MEK-->ERK inhibition suggests a treatment strategy for RAS-driven cancers. Nat. Med. 2019, 25, 620–627.
10. Dyall, J.; Coleman, C.M.; Hart, B.J.; Venkataraman, T.; Holbrook, M.R.; Kindrachuk, J.; Johnson, R.F.; Olinger, G.G., Jr.; Jahrling, P.B.; Laidlaw, M.; et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob. Agents Chemother. 2014, 58, 4885–4893.
11. Keyaerts, E.; Vijgen, L.; Maes, P.; Neyts, J.; Van Ranst, M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem. Biophys. Res. Commun. 2004, 323, 264–268.
12. Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020, 30, 269–271.
13. Browning, D.J. Pharmacology of Chloroquine and Hydroxychloroquine. In Hydroxychloroquine and Chloroquine Retinopathy; Springer: New York, NY, USA, 2014.
14. Leung, L.S.; Neal, J.W.; Wakelee, H.A.; Sequist, L.V.; Marmor, M.F. Rapid Onset of Retinal Toxicity From High-Dose Hydroxychloroquine Given for Cancer Therapy. Am. J. Ophthalmol. 2015, 160, 799–805 e1.
15. Michaelides, M.; Stover, N.B.; Francis, P.J.; Weleber, R.G. Retinal toxicity associated with hydroxychloroquine and chloroquine: Risk factors, screening, and progression despite cessation of therapy. Arch. Ophthalmol. 2011, 129, 30–39.
16. Offerhaus, J.A.; Wilde, A.A.M.; Remme, C.A. Prophylactic (hydroxy)chloroquine in COVID-19: Potential relevance for cardiac arrhythmia risk. Heart Rhythm. 2020, 17, 1480–1486.
17. Furst, D.E. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus 1996, 5 (Suppl. 1), S11–S15.