# Hydroxychloroquine

Chloroquine (CQ) is a quinoline-based drug

## Indications

Widely used for the prevention and treatment of malaria. More recent studies have provided evidence that this drug may also harbor antitumor properties, whereby CQ possesses the ability to accumulate in lysosomes and blocks the cellular process of autophagy.

### Glioma

Golden et al. set out to investigate whether CQ analogs, in particular clinically established antimalaria drugs, would also be able to exert antitumor properties, with a specific focus on glioma cells.

Toward this goal, they treated different glioma cell lines with quinine (QN), quinacrine (QNX), mefloquine (MFQ), and hydroxychloroquine (HCQ) and investigated endoplasmic reticulum (ER) stress-induced cell death, autophagy, and cell death.

All agents blocked cellular autophagy and exerted cytotoxic effects on drug-sensitive and drug-resistant glioma cells with varying degrees of potency (QNX > MFQ > HCQ > CQ > QN). Furthermore, all quinoline-based drugs killed glioma cells that were highly resistant to temozolomide (TMZ), the current standard of care for patients with glioma. The cytotoxic mechanism involved the induction of apoptosis and ER stress, as indicated by poly(ADP-ribose) polymerase (PARP) cleavage and CHOP/GADD153. The induction of ER stress and resulting apoptosis could be confirmed in the in vivo setting, in which tumor tissues from animals treated with quinoline-based drugs showed increased expression of CHOP/GADD153, along with elevated TUNEL staining, a measure of apoptosis.

Thus, the antimalarial compounds investigated in this study hold promise as a novel class of autophagy inhibitors for the treatment of newly diagnosed TMZ-sensitive and recurrent TMZ-resistant gliomas [1)].

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Besides the standard therapeutic drug temozolomide (TMZ), quinoline-based antimalarial drugs such as hydroxychloroquine (HCQ) and BH3 mimetics such as AT101 were considered as possible drugs for Glioblastoma therapy.

METHODS: We investigated the effects of sequentially applied single and combined TMZ, HCQ and AT101 treatments in a long-term stimulation Glioblastoma in vitro model. We performed all investigations in parallel in human astrocytes and two differentially TMZ-responsive human Glioblastoma cell lines and adjusted used drug concentrations to known liquor/plasma concentrations in patients. We determined amounts of dead cells and still remaining growth rates and depicted our results in a heatmap-like summary to visualize which sequential long-term treatment schedule seemed to be most promising.

RESULTS: We showed that sequential stimulations yielded higher cytotoxicity and better tumor

growth control in comparison to single TMZ treatment. This was especially the case for the sequences TMZ/HCQ and TMZ + AT101/AT101 which was as effective as the non-sequential combination TMZ + AT101. Importantly, those affected both less and more TMZ-responsive glioma cell lines, whilst being less harmful for astrocytes in comparison to single TMZ treatment.

CONCLUSIONS: Sequential treatment with mechanistically different acting drugs might be an option to reduce side effects in long-term treatment, for example in local administration approaches [2)].

## Hydroxychloroquine overcomes cabergoline resistance in a patient with Lactotroph Pituitary neuroendocrine tumor

A 22-year-old man complaining erectile dysfunction underwent transsphenoidal surgery for a 2.7 cm sellar mass with total resection and was confirmed at pathology to have a lactotroph pituitary neuroendocrine tumor (PiNET). Postoperatively, the patient's PRL remained at high level and therefore accepted high-dose dopamine receptor agonist (DA) therapy. After over 3 months of bromocriptine (BRC) (15mg/day) and over 3 years of cabergoline (CAB) (3mg/week) therapy, the patient's prolactin (PRL) never achieved long-term normalization. He was diagnosed with DA-resistant lactotroph PitNET.

Method: In this study, the patient was given hydroxychloroquine (HCQ) (200 mg/d) and CAB (3 mg/w) in combination for four months. His PRL level was tested by blood test every month.

Results: Taking the combination therapy of HCQ and CAB, the patient's uncontrolled PRL level was normalized within one month and was maintained at the normal level thereafter. Pituitary magnetic resonance imaging (MRI) images with enhancement showed no recurrence. The patient also regained normal sexual function.

Discussion: This is the first report on the combination of HCQ with CAB for the effective treatment of DA-resistant lactotroph pituitary neuroendocrine tumor [3)].

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2)
Adamski V, Schmitt C, Ceynowa F, Adelung R, Lucius R, Synowitz M, Hattermann K, Held-Feindt J. Effects of sequentially applied single and combined temozolomide, hydroxychloroquine and AT101 treatment in a long-term stimulation glioblastoma in vitro model. J Cancer Res Clin Oncol. 2018 Jun 1. doi: 10.1007/s00432-018-2680-y. [Epub ahead of print] PubMed PMID: 29858681.
3)
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