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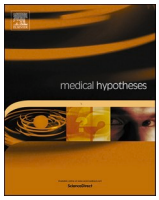

Can chloroquine/hydroxychloroquine prove efficient in cancer cachexia? A hypothesis in the era of COVID-19

Miroslaw Kiedrowski [a,b,*], Przemyslaw Kapala [a], Marlena Kiedrowska [c], Anna Skoczynska [c], Aleksandra Czerw [d], Andrzej Deptała [b,e]

[a] Ewdomed Ewa Szulecka Foundation and Home Hospice, Al. Wojska Polskiego 6, 05-520 Konstancin-Jeziorna, Poland
[b] Clinical Department of Oncology and Hematology, Central Clinical Hospital of the Ministry of the Anterior and Administration in Warsaw, ul. Woloska 137, 02-507 Warsaw, Poland
[c] Department of Epidemiology and Clinical Microbiology, National Medicines Institute, Chełmska 30/34, 00-725 Warsaw, Poland
[d] Department of Health Economics and Medical Law, Faculty of Health Sciences, Medical University of Warsaw, ul. Zwirki i Wigury 61, 02-091 Warsaw, Poland
[e] Division of Cancer Prevention, Faculty of Health Sciences, Medical University of Warsaw, ul. Zwirki i Wigury 61, 02-091 Warsaw, Poland

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ABSTRACT

Cancer cachexia (CC) is a progressive loss of muscle mass (with or without a decrease of adipose tissue). Gradual deterioration of the patient's fitness is resistant to nutritional intervention. The biochemical foundation of observed catabolism, detrimental protein, and energy balance is complex. However, the generalized inflammatory response plays a vital role. It is a kind of cytokine storm, which involves increased activity of TNF-α, IL-1, IL-6, and INF-γ. Pharmacological treatment of cachexia consists mainly of progestagens and glucocorticosteroids. Still, the assessment of new options limiting the harmful impact of cachexia could be beneficial. Chloroquine (CQ) and hydroxychloroquine (HCQ) are old antimalarial agents endowed with immunomodulatory properties. Being potent autophagy inhibitors, they could lead to a form of intracellular starvation in both cytokine-releasing cells and cancer cells, thus limiting the harmful impact of CC. CQ and HCQ are also efficient in particular connective tissue disorders. They have gained special attention since the World Health Organization announced the coronavirus disease 2019 (COVID-19) pandemic. According to initial reports, people with a severe inflammatory reaction showed significant benefits. Possibly they could not be attributed to the antiviral activity alone. It is worth noting that the cytokine storm in COVID-19, connective tissue disorders, and cancer cachexia share some similarities. Therefore, we hypothesize that low doses of CQ/HCQ may prove efficient in cancer cachexia.

Introduction

Cancer cachexia (CC) is a result of insufficient food intake, reduced anabolism, and increased catabolism. It reduces the vital forces of the affected person and significantly affects the quality of life. The cytokine storm (TNF-α, IL-1, IL-6, INF-γ), energy-inefficient processes (especially the Cori cycle), myostatin, and zinc-α2-glycoprotein overactivity, insulin resistance, and the consumption of energy substrates by cancer tissue constitute the biochemical basis of the decay processes [1]. The pro-inflammatory cytokine profile also occurs in connective tissue disorders [2,3]. The emergence of the SARS-CoV-2 pandemic re-emphasized the importance of cytokine storms in the etiology of debilitating and frequently lethal conditions. Old antimalarial drugs – chloroquine (CQ) and hydroxychloroquine (HCQ) – proved efficient in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [4]. According to some preliminary studies, they also seemed beneficial in COVID-19 – a syndrome developing in some patients with the SARS-CoV-2 infection [5–8]. Although initial enthusiasm for their use has diminished significantly, clinical trials are still underway in many countries. Despite the unrelated etiologies, the cytokines involved in the inflammatory response in cachexia, connective tissue diseases, and COVID-19 are similar [9].

The hypothesis

Although the etiology of CC is multifactorial and unclear, the cytokine storm is essential. This term was first employed to describe an impressively powerful activation of the immune system leading to graft-

* Corresponding author at: Ewdomed Ewa Szulecka Foundation and Home Hospice, Al. Wojska Polskiego 6, 05-520 Konstancin-Jeziorna, Poland.
E-mail address: mkiedrow@mp.pl (M. Kiedrowski).

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versus-host disease [10]. Over the years, the term was increasingly used in the medical literature to describe pronounced and frequently life-threatening immune system responses in many conditions. Many classes of compounds are involved in cytokine storms, including:

- interferons – a family of cytokines binding with specific receptors, which results in increased expression of antiviral and immunomodulatory proteins,
- tumor necrosis factor α (TNF-α) - a pyrogen cytokine released in the acute phase of infections, and associated with many inflammatory and autoimmune conditions,
- interleukins – involved in immune cell differentiation, activation, traffic, and production of secondary cytokines [11].

The significant effectiveness of anti-inflammatory agents – glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and omega-3 fatty acids – indicates that retuning the immune system and cytokine profile may reduce the detrimental impact of cachexia. The cytokine storms in CC, connective tissue disorders and COVID-19 share some similarities. Both chloroquine (CQ) and hydroxychloroquine (HCQ) seem beneficial in the latter two. Moreover, their long-term safety profile is well-known; connective-tissue disorders are chronic and usually incurable, requiring prolonged use of the drugs. Modulating a warped inflammatory reaction is crucial in the CC. Still, other CQ/HCQ properties could be involved. Reducing the lysosomes' acidity and subsequently influencing autophagy may lead to multiple biological consequences at the intracellular and higher levels. The question is whether CQ/HCQ could also be utilized in CC, especially in low doses, and combined with drugs of proven efficacy. Thus, we hypothesize that low doses of both CQ and HCQ may prove efficient in cancer cachexia, especially when combined with well-known agents (progestagens, corticosteroids) and nutritional intervention.

Evaluation of the hypothesis and discussion

According to the most widely accepted framework, there are three criteria to recognize cancer cachexia: weight loss >5% over the past six months, a body mass index <20 and weight loss >2%, or an appendicular skeletal muscle index consistent with sarcopenia and weight loss >2%. The same consensus distinguishes three stages of CC, namely pre-cachexia, cachexia, and refractory cachexia [12]. So far, few interventions have confirmed their effectiveness in the treatment of CC. These include progestagens, glucocorticosteroids, and some non-steroidal anti-inflammatory drugs (NSAIDs) [13–16]. The use of other agents is either not recommended or based on low-quality evidence. Glucocorticosteroids are endowed with pleiotropic properties. They inhibit the synthesis and release of many pro-inflammatory cytokines. They also enhance the neuropeptide Y level and reveal a rapid appetite improvement. Their prolonged use, however, is problematic. It is associated with many side effects (e.g., the risk of gastrointestinal bleeding, post-steroid myopathy, hyperglycemia) [17]. NSAIDs also diminish inflammation, lead to BMI and lean body mass improvement, improve quality of life, and reduce fatigue [16]. Their potential gastrointestinal toxicity limits the broader use of NSAIDs. It seems that omega-3 fatty acids reduce IL-1 and TNF-α concentrations. They inhibit glucocorticosteroid-dependent lipolysis, although, according to a systematic review by Dewey et al., they did not prove efficient [18]. It is readily apparent that many drugs used in CC are, in fact, anti-inflammatory agents.

Chloroquine was discovered over eight decades ago. Despite its antimalarial activity, it achieved a prominent place as an anti-inflammatory agent in connective tissue diseases. A derivative synthesized somewhat later – hydroxychloroquine – soon became favored due to its superior safety profile [19]. The detailed mechanism of action of those agents is unclear. They inhibit A2 phospholipase, lead to a decrease in excitation of CD4 lymphocytes, inhibit the release of cytokines, and limit antibody production. The impact of CQ/HCQ on the cytokine storm is presumably a manifestation of other actions at the subcellular and molecular levels. Thus, several other properties may be of crucial importance:

1. CQ and HCQ are weakly basic drugs, affecting the lysosomes. These small vesicles surrounded by a single lipid-protein membrane are endowed with H^+-ATPase pumps maintaining their internal pH around 5. They contain acid hydrolases, which can break down proteins, nucleic acids, carbohydrates, and fats. Lysosomes decompose substances absorbed by endocytosis. They also remove outdated and damaged cellular components, recovering organic substances by autophagy. Autophagy is performed by the formation of temporary sequestering structures (phagophores). They encapsulate components intended for turnover and turn into double-membrane autophagosomes fusing with lysosomes [20]. Autophagy is crucial in degrading large structures such as organelles and protein aggregates [21,22]. Alkalizing the lysosomes affects cellular digestion. Recently it was demonstrated that CQ inhibits autophagic flux by decreasing autophagosome-lysosome fusion [23]. Thus CQ and HCQ are autophagy inhibitors. We speculate that a relative shortage of substrates due to CQ/HCQ administration could limit the catastrophic overactivity of many cytokine-releasing cells involved in cancer cachexia.
2. Cancer cells utilize autophagy as an additional energy source, especially in an unfavorable metastatic environment. Some clinical trials have revealed the promising role of CQ as a novel oncological drug [24]. Both CQ and HCQ can increase sensitivity to radiation and certain chemotherapeutics. To date, they remain the only autophagy inhibitors approved by the Food and Drug Administration (FDA) [25–28]. Thus, we suppose that autophagy inhibition by CQ/HCQ could limit the harmful impact of cancer on the entire metabolism of affected people, including CC symptoms.

The SARS-CoV-2 pandemic outbreak in the year 2020 has motivated researchers worldwide to seek measures to reduce mortality in severely ill patients with COVID-19. Both CQ and HCQ have gained attention as drugs potentially effective in COVID-19, especially in patients with a pronounced cytokine storm, leading to multi-organ failure. Both CQ and HCQ seem active against SARS-CoV-2 in vitro. However, there are no high-quality data on efficacy and safety in clinical settings. Current usage indications, advocated in some national guidelines, are based on preliminary observations (mainly Chinese). Also, preliminary data on harmfulness appeared, and the US Food and Drug Agency (FDA) withdrew its consent to use these drugs in COVID-19 outside of the hospital setting and clinical trials [29]. Still, clinical trials are currently underway in several countries, including Burkina Faso, Egypt, Germany, Greece, Mexico, Pakistan, Poland, Vietnam, and the United States [30]. It seems that the antiviral activity of CQ/HCQ depends on interfering with endocytosis and membrane fusion, similarly to the postulated anti-cachectic activities. Also, CQ/HCQ inhibits ACE-2 receptor glycosylation, thus restricting the virus penetration into the cell. By alkalizing endocytic vesicles, they restrain endocytosis and proteolysis. The unfavorable clinical course of COVID-19 is associated with high concentrations of pro-inflammatory cytokines, especially IL-6 [31,32]. This finding suggests that excessive activation of the immune system in COVID-19 may be catastrophic. Thus, immunomodulatory properties contribute to the beneficial effect of CQ/HCQ [33,34].

To date, there are no empirical data concerning CQ/HCQ utilization in CC. The most reliable way to test our hypothesis would be to perform a double-blinded randomized clinical trial (RCT). Adult participants with cachexia/refractory cachexia recruited, first of all, from stationary hospices and able to swallow tablets would be randomized to two arms. The first arm would receive the standard treatment (e.g., progestagens or corticosteroids plus oral nutritional support) and the tested drug (preferably HCQ). In the second arm, patients would take the same therapeutic regimen plus placebo. Certain doubts arise, however. CQ or

HCQ are highly active substances exhibiting adverse effects. The most common are nausea, vomiting, and diarrhea [35,36]. Some of them could lower the quality of ending life, which could be especially undesirable in this particularly sensitive group. Most of them are dose-dependent and usually appear with loading doses of 800 mg of HCQ daily [37]. Other common adverse effects – e.g., retinopathy – are irrelevant in this group of participants due to the short life expectancy [38]. Thus, low doses of drugs should be tested first (e.g., 250 mg CQ/200 mg HCQ daily). The proposed end-points could be weight change, specific marker concentrations (e.g., C-reactive protein, pro-inflammatory cytokines), and survival time. Also, standardized self-assessment questionnaires such as EORTC QLQ-30 would help assess the quality of life and multi-dimensional functioning of participants [39].

Before conducting an RCT, we propose a comparative observational study. Comparing the CC in patients already treated with CQ/HCQ due to previously diagnosed autoimmune conditions with the majority without such burdens could be quite informative. However, acquiring a group of the right size would be problematic. Thus, a multi-center observational study could help to achieve sufficient power. Still, there is a risk that the assessment of cachexia symptoms could be biased by the overlapping of cancer and autoimmune disorders' influence. Existing benefits might then go unnoticed.

Consequences of the hypothesis

The incidence of CC depends on the tumor type and clinical staging. In pancreatic or gastric cancer patients, its frequency exceeds 80%, while in the lung, colon, or prostate, it is about 50% [40]. Cachexia contributes to at least 20% of cancer-associated deaths. It lowers the quality of life and limits therapeutic options in many patients [41]. Medical therapy – chemotherapy (especially platinum-based) and radiotherapy – may also contribute to CC development [42]. Moreover, CC significantly increases the economic costs of medical care.

The COVID-19 pandemic became a trigger for our scientific considerations. Noticing common elements in the pathogenesis of such various conditions as CC, autoimmune diseases, and COVID-19 justifies the question about new applications for old drugs. Of note, the effectiveness of most drugs used to date diminishes over time in CC or is restricted due to their side effects. The progression of several cancers may be, however, accelerated by inflammation. A growing body of evidence indicates inflammation as a hallmark of disease that substantially contributes to the progression of malignancies [43]. It is reasonable to claim that cancer progression exacerbates cachexia, but at the same time, cachexia can accelerate cancer progression. In this situation, it seems conceivable that using old drugs – CQ/HCQ – could be associated with prolonged survival and improved quality of life. If efficacy is confirmed, the proposed treatment would also be cost-effective.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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