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# Chloroquine and hydroxychloroquine for cancer therapy

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**Abbreviations:** BCL2, B-cell CLL/lymphoma 2; BECN1, Beclin 1; CQ, chloroquine; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HCQ, hydroxychloroquine; ; NSCLC, non-small-cell lung carcinoma; PI3K, phosphoinositide-3-kinase; RCC, renal cell carcinoma; ROS, reactive oxygen species; WBRT, whole-brain radiation therapy

Macroautophagy (herein referred to as autophagy) is a highly conserved mechanism for the lysosomal degradation of cytoplasmic components. Autophagy is critical for the maintenance of intracellular homeostasis, both in baseline conditions and in the context of adaptive responses to stress. In line with this notion, defects in the autophagic machinery have been etiologically associated with various human disorders including infectious, inflammatory and neoplastic conditions. Once tumors are established, however, autophagy sustains the survival of malignant cells, hence representing an appealing target for the design of novel anticancer regimens. Accordingly, inhibitors of autophagy including chloroquine and hydroxychloroquine have been shown to mediate substantial antineoplastic effects in preclinical models, especially when combined with chemo- or radiotherapeutic interventions. The pharmacological profile of chloroquine and hydroxychloroquine, however, appear to involve mechanisms other than autophagy inhibition. Here, we discuss the dual role of autophagy in oncogenesis and tumor progression, and summarize the results or design of clinical studies recently completed or initiated to evaluate the therapeutic activity of chloroquine derivatives in cancer patients.

## Introduction

The term autophagy (from ancient Greek, αυτο/auto = "self" + φαγος, φαγεῖν/phagein = "to eat"; i.e., self-eating) cumulatively refers to a group of catabolic mechanisms involved in the maintenance of cell and tissue homeostasis in all eukaryotes. Autophagy plays an essential role in multiple physiological processes, including development, differentiation, normal growth and immunity.[1-3] In line with this notion, defects in the executioner and regulatory mechanisms of autophagy have been involved in the etiology of a panel of clinically relevant disorders, including infectious, neurodegenerative and neoplastic diseases.[1,4-6]

Mammalian cells are endowed with at least 3 distinct autophagic pathways: macroautophagy, microautophagy, and chaperone-mediated autophagy.[7,8] Macroautophagy (herein referred to as autophagy, for the sake of simplicity) is a highly conserved mechanism responsible for lysosomal degradation of cytoplasmic components, including invading pathogens, cytotoxic protein aggregates and damaged organelles.[2,8] Autophagy relies on a peculiar double-membraned vesicle commonly known as autophagosome.[9] Autophagosomes are generated in the cytoplasm from precursor organelles known as phagophores, which progressively enwrap the material to be degraded and – upon closure – fuse with lysosomes.[9-11] This activates $H^+$ pumps to lower the pH of the lysosomal lumen and hence unleash the catabolic activity of lysosomal hydrolases. The products of the degradation of the autophagic cargo eventually reach the cytosol through lysosomal permeases, hence becoming available for reuse in biosynthetic metabolic circuitries.[12] A detailed description of the autophagic machinery and its regulators goes largely beyond the scope of the present Trial Watch and can be found in references 8, 9, and 13–18.

Although autophagosomes were initially believed to take up cytoplasmic material in a relatively non-selective fashion, a growing body of evidence has revealed the existence of highly specialized autophagic pathways that selectively recognize their substrates. As a standalone example, mitophagy has been shown to specifically eliminate superfluous or damaged mitochondria, hence operating as a key quality control mechanism.[19-21]

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Beside operating to preserve cellular homeostasis in physiological conditions, autophagy responds to a wide variety of perturbations including nutrient and growth factor deprivation, hypoxia, pathogen invasion, and exposure to cytotoxic agents.[2,22] In this setting, autophagy generally orchestrates a cell-wide adaptive response that aims at (1) physically removing the initiating stimulus (when possible), (2) coping with its cytotoxic effects, and (3) re-establishing cellular homeostasis. Thus, autophagy most often constitutes a cytoprotective response allowing cells to adapt to stressful conditions.[23,24] However, in a limited number of scenarios, including the development of *Caenorhabditis elegans*[25] and *Drosophila melanogaster* cells,[26-28] as well as the exposure of cancer cells to specific stimuli,[29-32] autophagy appears to mediate (at least in part) cell death. Only in such settings, i.e., when the pharmacological or genetic inhibition of the autophagic machinery delays (rather than accelerates) cell death, the term "autophagic cell death" should be employed to indicate a specific cell death subroutine.[24,33,34]

Along the lines of the Trial Watch series published on a monthly basis in OncoImmunology,[35-38] here we summarize the dual role of autophagy in oncogenesis and tumor progression and discuss recent clinical trials investigating the use of chloroquine (CQ), hydroxychloroquine (HCQ) in cancer patients. Importantly, although these agents were initially tested in oncological scenarios owing to their ability to inhibit autophagy, it is now clear that their therapeutic effects involve other mechanisms.[39-41]

## Autophagy and Cancer

A large body of evidence suggests that the relationship between autophagy and cancer is complex.[42,43] On the one hand, autophagy appears to inhibit malignant transformation, reflecting its capability to limit the accumulation of potentially oncogenic entities like depolarized mitochondria (which overproduce potentially genotoxic reactive oxygen species, ROS). On the other hand, autophagy supports the progression and metastatic dissemination of established tumors, increasing the ability of malignant cells to cope with adverse microenvironmental conditions like nutrient deprivation and hypoxia (two common denominators of rapidly growing solid tumors).

**Autophagy in oncogenesis**

Several distinct genetic manipulations that compromise (at least to some extent) the proficiency of the autophagic machinery have been shown to increase the propensity of laboratory animals to develop neoplastic lesions, be them spontaneous, genetically driven or chemically induced. This applies to the monoallelic loss of Beclin 1 (*Becn1*), coding for a key subunit of the class III phosphoinositide-3-kinase (PI3K) complex that controls the formation and elongation of autophagosomes;[44,45] to the whole-body absence of autophagy related 4C, cysteine peptidase (*Atg4c)*, encoding a protease involved in one of the conjugation systems required for autophagy;[46] the whole-body or tissue-specific deletion of *Atg5* and *Atg7*, coding for two of the components involved in the other of such conjugation systems;[47-50] as well as to the whole-body ablation of sequestosome 1 (*SQSTM1*), encoding an autophagic adaptor best known as p62.[51] Apparently at odds with these data, the ablation of RB1-inducible coiled-coil 1 (*Rb1cc1*), coding for a component of the autophagic machinery also known as FIP200, has been reported to inhibit the development of mammary carcinomas in mice expressing the polyoma middle T antigen under the control of the mouse mammary tumor virus long-terminal repeat.[52] Along similar lines, the monoallelic loss of *Becn1* has been shown to limit mammary tumorigenesis driven by partner and localizer of BRCA2 (PALB2).[53] However, it remains to be determined whether such effects truly depend on autophagy rather than reflecting indirect alterations of the tumor protein p53 (TP53, best known as p53) system.[54,55] FIP200 is indeed known to influence the stability of p53 and the oncogenic effects of the *Becn1*$^{+/-}$ were lost in a conditionally *Trp53*-null background.[53,56,57]

Further demonstrating the oncosuppressive functions of autophagy, the monoallelic deletion of *BECN1* has been detected in a large fraction (more than 40%) of human breast, ovarian and prostate carcinomas,[1,58,59] while mutations in *ATG5* and *ATG12* have been documented in a proportion of colorectal neoplasms.[60] Along similar lines, the expression levels of ATG5 and BECN1 are altered in various types of cancer,[61-70] leading some to speculate that the proficiency of the autophagic machinery may predict the propensity of a specific tissue to undergo malignant transformation. However, unambiguous clinical data in support of this hypothesis are missing.

Of note, several bona fide oncosuppressor proteins like phosphatase and tensin homolog (PTEN) and serine/threonine kinase 11 (STK11, best known as LKB1) stimulate autophagy, while multiple oncogenic pathways inhibit it.[43] For instance, this applies to the hyperactivation of the PI3K-AKT1 signal transduction cascade,[71-75] to mutations that render the epidermal growth factor receptor (EGFR) constitutively active,[76] as well as to the overexpression of anti-apoptotic Bcl-2 family members like B-cell CLL/lymphoma 2 (BCL2) itself and BCL2-like 1 (BCL2L1, best known as BCL-$X_L$).[43,77]

The current hypothesis is that the suppression of autophagy would promote oncogenesis by (1) altering bioenergetic metabolism and favoring the establishment of oxidative stress, two strictly interdependent processes resulting from impaired mitochondrial turnover;[42,78-80] (2) fostering genomic instability, at least in part as a consequence of oxidative stress;[81-83]) (3) impairing oncogene-induced senescence, a mechanism that permanently blocks the proliferation of malignant cells while allowing for their elimination by the immune system;[68,84-87] and (4) favoring the accumulation of p62-containing protein aggregates, which deliver oncogenic signals upon the activation of the transcription factor nuclear factor, erythroid 2-like 2 (NFE2L2, best known as NRF2).[88,89] Finally, autophagy appears to be critically involved in immunogenic cell death, a peculiar type of apoptosis that is associated with the elicitation of an adaptive immune response.[37,90,91] Thus, autophagy-deficient malignant cells are less prone than their autophagy-competent counterparts to be recognized and eliminated by the immune system,[92] a situation that impacts both oncogenesis and tumor progression (see below). Along similar lines, recent data indicate that the ablation of *Atg5*

accelerates *KRAS*-driven oncogenesis while favoring tumor infiltration by immunosuppressive $CD4^+CD25^+FOXP3^+$ regulatory T cells.[48] Defects in the autophagic machinery might therefore promote oncogenesis not only by impairing the capacity of cells to cope with potentially tumorigenic stimuli, but also by compromising oncosuppressive pathways that are mediated by the tumor microenvironment.

**Autophagy in tumor progression**

It is now clear that established neoplastic lesions benefit from the preservation (or reactivation) of autophagic functions. Even in the absence of therapy, indeed, hematological and (especially so) solid malignancies are exposed to unfavorable microenvironmental conditions, including a limited availability of nutrients and low oxygen concentrations. In line with this notion, cancer cells from poorly vascularized, hypoxic tumor regions contain elevated amounts of autophagosomes, allowing them to deal with limited oxygen supplies.[93] Moreover, several cell lines obtained from established cancers not only are characterized by increased levels of autophagy in baseline conditions, but also appear to require an elevated autophagic flux for the maintenance of metabolic functions and proliferation.[80,94,95] These observations indicate that cancer cells rely on autophagy (at least to some extent) for coping with the metabolic and oxidative load imposed by the malignant phenotype.

Accumulating evidence corroborates the notion that autophagy promotes the progression of established cancers. First, the downregulation of Atg5 induces extensive central necrosis in $Tsc2^{-/-}$ xenografts, while the heterozygous loss of *Becn1* limits the development of macroscopic renal tumors in $Tsc2^{+/-}$ mice.[96] Second, the tissue-specific deletion of *Atg5* or *Atg7* reportedly arrests the progression of benign hepatomas to hepatocellular carcinomas (HCCs),[47] of $KRAS^{G12D}$-driven pancreatic lesions to overtly malignant pancreatic ductal adenocarcinomas,[50] as well as of $KRAS^{G12D}$- or $BRAF^{V600E}$-driven pulmonary adenomas to lung adenocarcinomas,[48] sometimes diverting it to the formation of relatively benign oncocytomas.[49,97] Apparently in contrast with these observations, a tyrosine phosphomimetic variant of BECN1 has been shown to favor the growth, progression and resistance to therapy of non-small cell lung carcinoma (NSCLC) xenografts expressing constitutively active EGFR, an effect that correlated with a decrease in autophagic flux.[76] However, it is difficult to determine to which extent this stems from the inhibition of autophagy as opposed to the increased availability of antiapoptotic BCL2-like proteins caused by BECN1 phosphorylation.[75,98]

The current view is that autophagy facilitates the progression of established neoplasms by (1) favoring their adaptation to adverse microenvironmental conditions, including limited nutrient availability and hypoxia; (2) preserving mitochondrial functions, both as it controls the quality of the mitochondrial network and as it provides metabolic substrates for mitochondrial metabolism; and (3) limiting the accumulation of potentially cytotoxic entities, such as ROS, which is accrued in malignant cells owing to both intracellular and extracellular alterations.

## CQ Derivatives in Cancer Therapy

**Preclinical and clinical studies**

The notion that neoplastic cells of diverse histological origin require a proficient autophagic machinery to actively proliferate[53,80,97,99-101] in spite of adverse microenvironmental conditions, be them endogenous[102,103] or elicited by therapy,[74,104-116] has rendered this catabolic pathway an attractive target for the development of novel antineoplastic agents.[42,117-119] Thus, throughout the past decade, distinct approaches based on the inhibition of autophagy have been conceived and evaluated (in vitro and in vivo) for their ability to (1) mediate therapeutic effects as standalone interventions, or (2) boost the antineoplastic activity of conventional or targeted chemotherapeutics. In these studies, autophagy was disabled either genetically, through the knockout of autophagy-relevant genes or the knockdown of their products,[93,106,120-126] or pharmacologically, by the administration of (1) lysosomotropic agents including CQ, HCQ, Lys0569 and monensin, all of which inhibit the fusion of autophagosomes with lysosomes and their degradation;[74,112,115,120,127-132] (2) class III PI3K inhibitors, such as 3-methyladenine, wortmannin, LY294002 and pyrvinium;[109,122,126,130,133-137] (3) the V-type ATPase inhibitor bafilomycin A1, which inhibits lysosomal acidification and hence the degradation of autophagosomes;[121,125,138] (4) spautin-1, which promotes the ubiquitination-dependent degradation of BECN1.[139-142] All these interventions have been shown to exert anticancer effects or to boost the activity of conventional antineoplastic regimens. However, the antineoplastic effects of CQ and HCQ stem in large part from the modulation of pathways other than autophagy.[39-41] These lysosomotropic agents are indeed very efficient at inducing lysosomal membrane permeabilization, hence initiating the mitochondrial pathway of apoptosis.[39,143] Moreover, CQ has recently been show to target cancer stem cells by inhibiting Janus kinase 2 (JAK2) signaling.[144] The precise reasons why neoplastic cells appear to be more sensitive to CQ and HCQ than their non-transformed counterparts, however, remain to be elucidated.

The therapeutic potential of CQ, which has been widely employed (and is currently approved by the US Food and Drug Administration, FDA) for the prophylactic treatment of malaria (source http://www.fda.gov), has been investigated in a double-blinded clinical trial involving 30 patients with glioblastoma multiforme (NCT00224978).[127] In this setting (a Phase III clinical trial), eligible patients with surgically confirmed glioblastoma were randomized to receive conventional chemotherapy and radiotherapy plus placebo or 150 mg/d CQ per os. Of note, although the study was insufficiently powered to detect a statistical difference in the survival rate of the study arms, CQ-receiving patients exhibited an improved mid-term survival as compared with their control counterparts.[127] CQ has also been evaluated for its ability to boost the therapeutic activity of whole-brain radiation therapy (WBRT) in 20 patients bearing intracranial metastases of various histological derivation (NCT01894633).[145] In the context of this single-cohort Phase II clinical study, CQ

**Table 1.** Clinical trials recently launched to evaluate the safety and efficacy of CQ derivatives in cancer patients*

| Agent | Indication(s) | Status | Phase | Notes | References |
|---|---|---|---|---|---|
| CQ | Brain metastases | Recruiting | II | Combined with whole brain | NCT01727531 |
| | Breast carcinoma | Recruiting | I | Combined with microtubular poisons | NCT01446016 |
| | | | I/II | As single agent | NCT01023477 |
| | Multiple myeloma | Recruiting | II | Combined with bortezomib and cyclophosphamide | NCT01438177 |
| | Pancreatic carcinoma | Recruiting | I | Combined with gemcitabine | NCT01777477 |
| | SCLC | Recruiting | I | Combined with RT, cisplatin and etoposide | NCT00969306 |
| | | Not yet recruiting | I | Combined with RT | NCT01575782 |
| | Advanced solid tumors | Not yet recruiting | I | Combined with carboplatin and gemcitabine | NCT02071537 |
| HCQ | Bone metastases | Recruiting | I | Combined with RT | NCT01417403 |
| | CML | Unknown | II | Combined with imatinib | NCT01227135 |
| | Colorectal carcinoma | Recruiting | I/II | Combined with bevacizumab and oxaliplatin-based chemotherapy | NCT01206530 |
| | | | II | Combined with bevacizumab, capecitabine and oxaliplatin | NCT01006369 |
| | GBM | Unknown | I/II | Combined with temozolomide and RT | NCT00486603 |
| | Glioma | Recruiting | II | Combined with RT | NCT01602588 |
| | HCC | Recruiting | I/II | Combined with TACE | NCT02013778 |
| | Multiple myeloma | Recruiting | I | Combined with cyclophosphamide, dexamethasone and rapamycin | NCT01689987 |
| | | Unknown | I/II | Combined with bortezomib | NCT00568880 |
| | NSCLC | Active, not recruiting | I/II | Combined with bevacizumab, carboplatin and paclitaxel | NCT00933803 |
| | | Active, not recruiting | II | Combined with erlotinib | NCT00977470 |
| | | Recruiting | I/II | Combined with gefitinib | NCT00809237 |
| | | | II | Combined with bevacizumab, carboplatin and paclitaxel | NCT01649947 |
| | Melanoma | Recruiting | I | Combined with vemurafenib | NCT01897116 |
| | Pancreatic carcinoma | Active, not recruiting | I/II | Combined with gemcitabine | NCT01128296 |
| | | Active, not recruiting | II | Combined with abraxane and gemcitabine | NCT01978184 |
| | | Recruiting | I/II | Combined with gemcitabine | NCT01506973 |
| | | | II | Combined with capecitabine and RT | NCT01494155 |
| | Prostate carcinoma | Active, not recruiting | II | As single agent | NCT00726596 |
| | | Recruiting | II | Combined with abiraterone and ABT-263 | NCT01828476 |
| | Renal cell carcinoma | Recruiting | I | As single agent | NCT01144169 |
| | | | I/II | Combined with everolimus | NCT01510119 |
| | | | | Combined with IL-2 | NCT01550367 |
| | Soft tissue sarcoma | Recruiting | II | Combined with rapamycin | NCT01842594 |

Abbreviations: CML, chronic myeloid leukemia; CQ, chloroquine; HCQ, hydroxychloroquine; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; IL-2, interleukin-2; NSCLC, non-small cell lung carcinoma; RT, radiation therapy; SCLC, small cell lung carcinoma; TACE, transarterial chemoembolization.
*between 2007, January 1st and the date of submission.

**Table 1.** Clinical trials recently launched to evaluate the safety and efficacy of CQ derivatives in cancer patients* (continued)

| Agent | Indication(s) | Status | Phase | Notes | References |
|---|---|---|---|---|---|
| | Advanced solid tumors | Active, not recruiting | I | Combined with sunitinib | NCT00813423 |
| | | Recruiting | I | Combined with vorinostat | NCT01023737 |
| | | | | Combined with rapamycin or vorinostat | NCT01266057 |
| | | | | Combined with MK2206 | NCT01480154 |
| | | | | Combined with sorafenib | NCT01634893 |
| | | Unknown | I | Combined with temozolomide | NCT00714181 |
| | | | | Combined with temsirolimus | NCT00909831 |

Abbreviations: CML, chronic myeloid leukemia; CQ, chloroquine; HCQ, hydroxychloroquine; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; IL-2, interleukin-2; NSCLC, non-small cell lung carcinoma; RT, radiation therapy; SCLC, small cell lung carcinoma; TACE, transarterial chemoembolization. *between 2007, January 1st and the date of submission.

therapy (250 mg/day per os) was initiated 1 we before WBRT, and the primary endpoint was radiologic response. Five months after WBRT, 16 patients were evaluable, of which: 2 manifested a complete response, 13 a partial response and 1 disease stabilization. No treatment-related Grade 3/4 toxicities were recorded, and mean overall survival was 8.9 mo.[145] As such a high intracranial disease control warrants further investigation, this clinical paradigm remains under investigation (see below).

The safety and antineoplastic activity of HCQ, a CQ derivative approved by the US FDA as an antimalarial drug as well as for the management of (chronic, discoid or systemic) lupus erythematosus and acute or chronic rheumatoid arthritis (source http://www.fda.gov), has recently been evaluated in 20 patients with metastatic pancreatic cancer that failed to respond to conventional treatments (NCT01273805).[146] In this setting (a Phase II clinical trial), patients received 400 (n = 10) or 600 (n = 10) mg HCQ twice daily as a single therapeutic agent. Although this regimen was well tolerated (only 2 patients developed treatment-related Grade 3/4 side effects), only 2 individuals (10%) did not exhibit disease progression 2 mo after the initiation of HCQ.[146] HCQ has also been investigated as a means to boost the therapeutic profile of erlotinib (an FDA-approved chemical inhibitor of EGFR)[147-150] in 27 subjects with advanced NSCLC (NCT01026844).[114] In this 2-arms Phase I study, 8 patients were treated with HCQ only, while 19 received HCQ plus erlotinib. Only one patient experienced a partial response to erlotinib plus HCQ, but no dose-limiting toxicities related to HCQ were documented, and the authors recommended the use of 1000 mg/day HCQ in combination with 150 mg/day erlotinib for a subsequent Phase II study.[114]

Altogether, these preclinical and clinical observations suggest that CQ and HCQ may not mediate significant therapeutic benefits as standalone interventions but may exacerbate the effects of conventional anticancer agents.

**Ongoing clinical trials**

When this Trial Watch was being redacted (May 2014), official sources listed 39 ongoing clinical trials launched after 2007, January 1st to investigate the safety and therapeutic potential of CQ derivatives, either as a standalone therapeutic interventions or as part of combinatorial chemotherapeutic regimens, in cancer patients (http://www.clinicaltrials.gov/) (**Table 1**). Of these trials, 8 involve CQ and 31 HCQ. Of note, the latter is generally preferred to the former owing to its tolerability and toxicity profile.[151,152]

The safety and antineoplastic activity of CQ derivatives as standalone chemotherapeutic interventions are being assessed (1) in subjects with breast ductal carcinoma in situ, who receive CQ per os for 1 mo prior to surgical tumor excision (NCT01023477); (2) in prostate cancer patients, who are treated with HCQ upon raise in the circulating levels of prostate-specific antigen (PSA) (NCT00726596); and (3) in individuals with primary renal cell carcinoma (RCC), who receive HCQ orally for 14 d before surgery (NCT01144169).

In a vast majority of ongoing clinical trials, CQ derivatives are given in combination with conventional chemo-, radio- or immunotherapeutic regimens. In particular, the safety and efficacy of CQ are being tested: (1) in subjects with advanced or metastatic breast carcinoma resistant to anthracycline-based chemotherapy,[37,90,91] who receive CQ in combination with microtubular poisons of the taxane or epothilone family[153-155] (NCT01446016); (2) in patients with Stage IV small cell lung carcinoma, who are treated with CQ in combination with conventional radiotherapy[156,157] (NCT01575782) and/or DNA-damaging chemotherapeutic regimens including standard-dose cisplatin-etoposide[158-161] (NCT0969306); (3) in subjects with multiple myeloma, receiving CQ in combination with cyclophosphamide, an immunogenic alkylating agent,[162,163] and bortezomib (NCT01438177); (4) in pancreatic cancer patients, who receive CQ in combination with the immunostimulatory chemotherapeutic gemcitabine[164,165] (NCT01777477); (5) in patients with advanced solid tumors, receiving CQ together with gemcitabine and carboplatin (a cisplatin-derived DNA-damaging agent)[166] (NCT02071537); and (6) in subjects bearing brain metastases from various neoplasms, who receive a short course of CQ in combination with WBRT (NCT01727531).

Moreover, HCQ is being investigated as means to improve the therapeutic profile of (1) neoadjuvant gemcitabine and/or paclitaxel protein-bound particles (Abraxane®), in individuals

affected by advanced pancreatic carcinoma (NCT01506973; NCT01128296; NCT01978184); (2) the alkylating agent temozolomide,[167-169] in patients with metastatic or unresectable solid tumors (NCT00714181); (3) radiation therapy, in patients with high grade glioma (NCT01602588) or bearing bone metastases of diverse histological derivation (NCT01417403); (4) temozomolide and radiation therapy, in individuals with newly diagnosed glioblastoma multiforme (NCT00486603); (5) capecitabine (an antimetabolite currently employed for the treatment of several neoplasms)[170] plus radiation therapy, in patients with resectable pancreatic cancer (NCT01494155); (6) capecitabine, oxaliplatin (an FDA-approved cisplatin derivative),[171,172] and bevacizumab (a monoclonal antibody specific for vascular endothelial growth factor, VEGF),[38,173-175] in subjects with metastatic colorectal carcinoma (NCT01006369); (7) paclitaxel (an FDA-approved microtubular poison of the taxane family), carboplatin and bevacizumab, in NSCLC patients (NCT00933803; NCT01649947), (8) an oxaliplatin-based chemotherapeutic regimen combined with bevacizumab, in individuals affected by colorectal carcinoma (NCT01206530); (9) transarterial chemoembolization (TACE),[176,177] in patients with unresectable HCC (NCT02013778); (10) the AKT1 inhibitor MK2206,[178] in patients affected by advanced solid malignancies (NCT01480154); (11) rapamycin and/or vorinostat, in subjects with refractory soft tissue sarcomas (NCT01842594) or other solid tumors (NCT01023737; NCT01266057); (12) temsirolimus (an FDA-approved rapamycin derivative that also exerts antineoplastic effects by inhibiting mechanistic target of rapamycin, MTOR),[179] in patients with metastatic solid tumors that failed to respond to conventional therapeutic regimens (NCT00909831); (13) everolimus (yet another rapamycin-like molecule licensed by the US FDA), in individuals with advanced RCC (NCT01510119); (14) sirolimus, cyclophosphamide and dexamethasone, in patients with relapsed or refractory multiple myeloma (NCT01689987); (15) erlotinib or gefitinib (a chemical inhibitor of EGFR currently licensed by the US FDA),[148,180] in NSCLC patients (NCT00809237; NCT00977470); (16) imatinib (an FDA-approved inhibitor or BCR-ABL, KIT and platelet-derived growth factor receptor β),[181,182] in individuals with chronic myeloid leukemia (NCT01227135); (17) sorafenib or sunitinib (two multi-kinase inhibitor nowadays approved by the US FDA for the treatment of various solid tumors),[183-188] in patients with refractory and/or relapsed solid tumors (NCT00813423; NCT01634893); (18) bortezomib, in subjects with refractory and/or relapsed multiple myeloma (NCT00568880); (19) vemurafenib (an FDA-approved inhibitor of mutant BRAF),[189] in melanoma patients (NCT01897116); (20) ABT-263 (an experimental inhibitor of anti-apoptotic Bcl-2 family members)[143,190,191] and abiraterone (an FDA-approved antiandrogen),[192] in individuals with metastatic castration-resistant prostate cancer (NCT01828476); and (21) interleukin-2 (an immunostimulatory cytokine currently approved by the US FDA and other regulatory agencies for the treatment of metastatic forms of melanoma and RCC),[193,194] in patients with metastatic RCC (NCT01550367).

## Concluding Remarks

Accumulating evidence suggests that inhibiting autophagy may constitute an efficient means to improve the therapeutic profile of chemo-, radio- and immunotherapeutic anticancer regimens. However, autophagy not only sustains the survival of established neoplasm exposed to therapy, but also plays a key role in the maintenance of intracellular homeostasis in healthy tissues (de facto operating as an oncosuppressive mechanism),[42,43] and is required for the elicitation of innate and adaptive immune responses.[195] This implies that the whole-body inhibition of autophagy may, at least theoretically, favor the insurgence of treatment-related neoplasms as well as of other disorders (e.g., infectious diseases, neurodegenerative conditions) and promote some degree of immunosuppression. Moreover, the wide majority of autophagy inhibitors that have been investigated so far in clinical trials, in particular CQ and HCQ, influence lysosomal (and possibly non-lysosomal) processes other than autophagy.[39-41] Indeed, the therapeutic activity of HQ and HCQ appears to stem mainly from the modulation of autophagy-unrelated mechanisms. Finally, autophagy seems to promote, rather than antagonize, the therapeutic activity of specific antineoplastic agents.[76,196-200] Hence, the co-administration of autophagy inhibitors may decrease, rather than increase, the cytostatic/cytotoxic potential of a fraction of chemicals currently employed in anticancer therapy. Taken together, these notions suggest that modulating autophagy may constitute a powerful means to achieve superior antineoplastic effects, yet should be implemented with caution. Future studies will have to elucidate whether and how autophagy can be modulated in a tissue- or cell-restricted manner that is compatible with clinical applications, as well as if biomarkers that predict the propensity of specific cancer patient subsets to autophagy regulators exist. These discoveries as well as the identification of compounds that regulate autophagy in a highly specific manner will surely widen the clinical utility of this therapeutic paradigm.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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