Chloroquine as a promising adjuvant chemotherapy together with sunitinib

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Received: September 04, 2014
Published online: October 15, 2014

Chloroquine - a clinically available and cheap antimalarial drug - might have potential usefulness as adjuvant chemotherapy when combined with sunitinib, reports a preclinical study recently published online in Chemico-biological Interactions. Just few years after its FDA approval to be used in imatinib resistant gastrointestinal tumor, renal carcinoma and pancreatic neuroendocrine tumor, light has been shed on the limited clinical efficacy of sunitinib as well as rapid development of resistant cells when used as monotherapy. Abdel-Aziz and her colleagues now showed that chloroquine augments sunitinib anticancer activity in vitro human cancer cell lines of breast, colorectal, cervical, laryngeal, liver and prostate origin and in vivo in murine Ehrlich ascites carcinoma tumor model. Furthermore, chloroquine interrupted autophagic flux which was induced by sunitinib. They noted that chloroquine when combined with sunitinib showed further activation of apoptosis in cancer cells. The observed synergy was associated with increased nitric oxide and reduced reactive oxygen species levels. The present findings warrant further studies to explore the safety profile of the combination regimen and its clinical usefulness in vivo and then in controlled clinical trials.

Keywords: sunitinib; chloroquine; autophagy; apoptosis; angiogenesis


Sunitinib malate (Sutent® capsules, by Pfizer) is a multikinase inhibitor [1] which is used for the treatment of imatinib-resistant gastrointestinal stromal tumor (GIST), metastatic renal cancer and progressive well-differentiated pancreatic neuroendocrine tumor [1]. Sunitinib competitively interacts with the intracellular ATP-binding site of tyrosine kinase receptors [2-4].

Despite its rapid approval to be used in three different indications, emerging studies described its undermined clinical usefulness as a single chemotherapeutic agent [5-7]. Several leading researchers and clinicians stressed the dire need to adopt “horizontal or vertical combination strategies” targeting multiple pathways or multiple points within a pathway respectively to control cancer. In this regards, several combination regimens have been suggested. Yin et al., (2014) showed that rapamycin when co-administered with sunitinib impeded breast cancer proliferation. Their combination, however, promoted tumor metastasis [8]. Sunitinib and curcumin have also been proposed as an effective antitumor combination to reduce the dose and risk of adverse effects of sunitinib [9]. As a potential mechanism of acquired resistance of cancer cells to sunitinib, Gotink et al., (2011) proposed “lysosomal sequestration” and hence hypothesized superior cytotoxic activity of sunitinib when combined with drugs interfering with lysosomal function as chloroquine [7].
Chloroquine has long been considered as the first choice for malaria treatment due to its efficacy, cheapness and tolerability [10]. Chloroquine is also used to treat autoimmune and inflammatory diseases [10-12]. Although the precise mechanism underlying the antimalarial effects of chloroquine remains undetermined, its weak-base lysosomotropic feature is believed to be a contributor [11-12]. Interestingly, several studies reported the efficacy of chloroquine in sensitizing cancer cells to radiotherapy as well as chemotherapy highlighting its value in improving cancer therapeutic strategies [12-15].

Accordingly, Abdel-Aziz et al., (2014) assessed the potential usefulness of chloroquine in enhancing the antiproliferative activity of sunitinib [7, 10-16]. In this study, chloroquine synergistically augmented sunitinib cytotoxicity in human hepatocellular, colorectal, cervical, laryngeal, breast and prostate cancer cells. The previous finding was also confirmed in vivo using murine Ehrlich carcinoma (EAC) solid and intraperitoneal models. Chloroquine enhanced sunitinib anticancer activity as evidenced by further reduction of tumor volume, tumor weight, EAC viability and proliferative cell nuclear antigen expression.

From a mechanistic perspective, chloroquine augmented sunitinib cytotoxicity via multiple approaches affecting autophagy, apoptosis, angiogenesis and redox state. The supra-additive cytotoxic activity evidenced in sunitinib and chloroquine combination was associated with blockade of sunitinib-induced autophagy (Figure.1). This may hint to the “cytoprotection adaptive” role of autophagy initiated by cancer cells in response to the cytotoxic stimuli of sunitinib. In this context, several studies described contradictory effects of sunitinib on autophagy [17-20]. This warrants further investigation to address this discrepancy. By reducing survivin protein level and activating caspase 3, chloroquine when combined with sunitinib triggered apoptosis in EAC cells (Figure.1). Although it has been thought that the antiautophagic and proapoptotic effects of chloroquine are responsible for its chemosensitizing effect, an interesting study by Maycotte, et al., (2012) ruled out this assumption [21]. This discrepancy can be addressed by genetically
abrating several autophagy and apoptosis genes to clarify whether the modulatory activity of chloroquine is mediated through modulation of autophagic and/or apoptotic machineries. The antiangiogenic capacity of sunitinib was also augmented by chloroquine (Figure 1). The antiangiogenic effect of chloroquine was reported to be via activating apoptosis in endothelial cells [22]. Sunitinib-chloroquine combination regimen also altered the redox state in EAC cells through increasing RNS and decreasing ROS levels (Figure 1).

In conclusion, cheap and clinically available drugs with favorable safety margin such as chloroquine could be re-introduced as an efficient chemosensitizer to enhance the antitumor activity of sunitinib. However, the toxicity/safety profiles and clinical effectiveness of such combination regimen necessitate further investigation in animal models and clinical trials.

Conflict of interests

The authors declare that they have no conflicting interests.

References