Effects of chloroquine and hydroxychloroquine on the sensitivity of pancreatic cancer cells to targeted therapies

Effects of Chloroquine and Hydroxychloroquine on the Sensitivity of Pancreatic Cancer Cells to Targeted Therapies

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Abstract

Approaches to improve pancreatic cancer therapy are essential as this disease has a very bleak outcome. Approximately 80% of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAC). PDAC is a cancer which is difficult to effectively treat as it is often detected late in the disease process. Almost all PDACs (over 90%) have activating mutations in the GTPase gene *KRAS*. These mutations result in constitutive KRas activation and the mobilization of downstream pathways such as the Raf/MEK/ERK pathway. Small molecule inhibitors of key components of the KRas/Raf/MEK/ERK pathways as well as monoclonal antibodies (MoAbs) specific for upstream growth factor receptors such insulin like growth factor-1 receptor (IGF1-R) and epidermal growth factor receptors (EGFRs) have been developed and have been evaluated in clinical trials. An additional key regulatory gene frequently mutated (~75%) in PDAC is the *TP53* tumor suppressor gene which controls the transcription of multiple genes involved in cell cycle progression, apoptosis, metabolism, cancer progression and other growth regulatory processes. Small molecule mutant TP53 reactivators have been developed which alter the structure of mutant TP53 protein and restore some of its antiproliferative activities. Some mutant TP53 reactivators have been examined in clinical trials with patients with mutant TP53 genes. Inhibitors to the TP53 negative regulator Mouse Double Minute 2 (MDM2) have been developed and analyzed in clinical trials. Chloroquine and hydroxychloroquine are established anti-malarial and anti-inflammatory drugs that also prevent the induction of autophagy which can have effects on cancer survival. Chloroquine and hydroxychloroquine have also been examined in various clinical trials. Recent studies are suggesting effective treatment of PDAC patients may require chemotherapy as well as targeting multiple pathways and biochemical processes.

1. Introduction

Pancreatic cancer accounts for many deaths world-wide (Muniraj et al., 2013; Siegel et al., 2013). The survival rate for pancreatic cancer is very poor. Pancreatic cancers are usually diagnosed late in the disease process often after metastasis to other sites. Pancreatic cancer is predicted to be one of the top five cancers resulting in death of the affected patient (Hu et al., 2021). Most (~85%) of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAC) (Orth et al., 2019).

1.1 Treatment of PDAC

Treatment options *for* PDAC patients are limited. One common therapy for PDAC is surgical removal of the diseased portion of the pancreas (Kommalapati et al., 2018). However, this is usually an ineffective therapy as the tumor frequently reappears and to complicate matters, the tumor may have metastasized to other organs. PDAC patients have a poor life expectancy after being diagnosed. Recent analysis has indicated that PDAC patients are predicted to have a short survival of less than a half a year and a 5-year median survival rate of approximately 10% (Ilic and Ilic, 2016). Upon transcriptomic analysis of PDAC patients with a different survival rates, the higher scoring patients, had more malignant tumors that contained mutations at *TP53*. The more malignant tumors were associated with unfavorable tumor microenvironment (TME) which included, lower infiltration of CD8-positive T cells and dendritic cells (Katsuta et al 2021).

Treatment with chemotherapeutic drugs is an effective approach to treat certain types of cancer patients. However, a common problem is the development of drug resistance. Sometimes treatment of certain cancers with chemotherapeutic drugs leads to the selection of drug resistance cancer stem cells (CSCs) from the initial tumor (McCubrey et al., 2008; Davis et al., 2014; Zhang et al., 2016; McCubrey et al., 2017). The CSCs may be less sensitive to chemotherapeutic drugs than the initial tumor cells. Chemotherapy is used to treat certain PDAC patients. However, treatment of PDAC patients with chemotherapy is usually a palliative

approach as opposed to curative approach and only some patients respond (Ruarus et al., 2018; Müller et al., 2021).

The base analogues gemcitabine and 5-fluorouracil (5FU) are two commonly used drugs to treat PDAC patients. In addition, the drug paclitaxel (currently, nab-paclitaxel which has albumin attached to it to increase the delivery of paclitaxel to the tumor), interacts with the microtubules during cellular division, is sometimes used. Many of these drugs slow tumor growth and relieve the pain in the PDAC patients caused by growth of the tumors. A summary of the chemotherapeutic drugs, immunotherapies, signal transduction inhibitors and repurposing of other drugs and vitamins examined in clinical trials with PDAC patients is presented in Table I.

1.2. Genes frequently mutated in PDAC.

Two of the most frequently mutated genes in PDAC are *KRAS* (~95%) and *TP53* (~75%) (Pu et al., 2019; Qian et al., 2020). Most *KRAS* oncogene mutations result in a constitutively active KRas protein which leads to stimulation of Raf/MEK/ERK, PI3K/PTEN/Akt/ERK and other pathways that can promote uncontrolled cell growth (Davis et al., 2014; Waters & Der., 2018). Altered *TP53* tumor suppressor activity can also lead to loss of cell cycle regulation, resistance to chemotherapeutic drugs and multiple biochemical pathways which also effect cell growth (Grant et al., 2016; Nakamura et al., 2016; Hayashi et al., 2019; McCubrey et al., 2022a).

Some *TP53* point mutations result in novel activities for the TP53 protein. This class of mutations are referred to as gain of function (GOF) mutations. An additional class of *TP53* mutations in PDAC results in deletion (either partial or full deletion) in one or both *TP53* alleles and the full length TP53 protein is not expressed. Certain mutant TP53 proteins with GOF properties will activate oncogenic Ras signaling (Escobar-Hoyos et al., 2020). Thus, the mutations at *TP53* and *KRAS* can conspire to result in uncontrolled proliferation of PDAC as well as other cancer types.

In addition, there are many other genes mutated or deregulated in PDAC. Two of the more commonly effected genes include *SMAD4* which encodes the small mothers against

decapentaplegic homolog 4 protein, which is a transcription factor and *CDKN2A* which encodes the cyclin-dependent kinase inhibitor 2A gene (the *CDKN2A* locus encodes both the p16 (INK4A) and the p14 (ARF) tumor suppressor proteins) (McCubrey et al., 2022a).

1.3. Combining Chemotherapy with Targeted Therapy

Many different signal transduction inhibitors have been evaluated to treat PDAC patients (Furuse and Nagashima. 2017; Qian et al., 2020). These approaches are usually ineffective as single agents. *BRAF* is also mutated in some PDAC patients. The effects of combining RAF inhibitors with chemotherapeutic drugs have been examined in PDAC patients which are mutant at *BRAF* and wild-type KRAS. MEK1 lies downstream of Ras and BRAF in the pathway. There is a case report which examined the effects of the MEK inhibitor cobimetinib on PDAC patients who had been previously treated with chemotherapeutic drugs: fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) (Ardalan et al., 2021). One patient was reported to have a complete response (CR) to the chemotherapeutic drugs combination and cobimetinib for at least 16 months.

There have been clinical trials examining the effects of combining chemotherapeutic drugs such as gemcitabine and oxaliplatin and the monoclonal antibody cetuximab (an epidermal growth factor receptor (EGFR) inhibitor) (Kullmann et al., 2011). A recent review summarizes the effects of many clinical trials of chemotherapy and various MoAb (Arias-Pinilla et al., 2011). Unfortunately, most of the clinical trials were not successful.

Chloroquine is an anti-malarial drug also used in the treatment of certain other diseases such as rheumatoid arthritis and sarcoidosis (Varisli et al., 2020). Chloroquine has been shown to block autophagy which has important effect on cancer cell survival (Candido et al., 2018). Autophagy has been proposed to be a therapeutic target in PDAC (Piffoux et al., 2021).

Autophagy is an important and complex process related to recycling of critical cell components and nutrients. It is especially important in the hostile tumor microenvironment where nutrients are limiting (Piffoux et al., 2021). Some studies have indicated that suppression of

autophagy can have anti-cancer effects while other studies suggest that induction of autophagy can have tumor promoting effect (Jung et al., 2016; Clark et al., 2017; Yun et al., 2020; Tracey et al., 2020).

There have been approximately twenty-two clinical trials with chloroquine and cancer patients (Pascolo, 2016). In some studies, the effect of treatment of PDAC patients with chloroquine and the chemotherapeutic drug gemcitabine have been examined in a clinical trial (Samaras et al., 2017). There are some clinical trials with MEK inhibitors and chloroquine. Two phase I/II trials have been performed with melanoma patients, that are mutated at the *BRAF* gene with chloroquine in combination with BRAF and MEK inhibitors (Mehnert et. al., 2022; Awada et al., 2022; Amaravadi., 2020).

Chloroquine may interact with mutant KRas in PDAC (Morgan et al 2014). Mutant KRas can influence autophagic flux in some cancers. The effects of combining chloroquine with chemotherapy and targeted therapy have been recently reviewed (Salimi-Jeda et al., 2022). There have been twenty-three clinic trials with chloroquine and cancer patients. Chloroquine has been combined with various chemotherapeutic drugs, signal transduction therapies and immunotherapies. In one trial with glioblastoma patients, chloroquine was combined with surgery, radiotherapy, chemotherapy and treated patients had a longer survival than untreated patients. Two patients had tumor remission for over two years while untreated patients did not survive longer than 22 months (Briceño et al., 2003; Sotelo et al., 2006). One study was performed with chloroquine and hydroxychloroquine and cabergoline (a natural product used to treat hyperprolactinemia) in pituitary tumors (Lin et al., 2017).

One clinical trial examined the effects of combining chloroquine and gemcitabine and chloroquine in PDAC patients (Samaras et al., 2017). This small exploratory study with nine PDAC patients examined the effects of chloroquine and gemcitabine. It was observed that the combination was well tolerated, and some positive effects were observed.

The effects of MEK inhibitors have been examined in seventeen clinical trials in patients with PDAC. Often MEK inhibitors were combined with the chemotherapeutic drug gemcitabine. Unfortunately, some studies have indicated no clinical benefit of the addition of the MEK inhibitors (Infante et al., 2014; Chung et al., 2017; Van Cutsem et al., 2018).

The effects of IGF-1R inhibitors (usually MoAbs) in combination with chemotherapeutic drugs (usually gemcitabine) have been examined in PDAC patients in five clinical trials (Abdel-Wahab et al., 2018). The effects of targeting the EGFR/HER2 have been examined with both MoAbs directed to EGFR/HER2 and kinase inhibitors in approximately 21 clinical trials with PDAC patients.

1.4. Emerging Approaches to Potentially Treat PDAC Patients

Until relatively recently there were limited approaches to effectively treat the mutant KRas and TP53 proteins and they were often referred to as undruggable targets (Huang et al., 2021; Sallman., 2020; Sallman et al., 2021). Recently, novel of mutant KRas inhibitors have been developed and are being examined in clinical trials especially with colorectal cancer patients (Canon et al., 2019; Hallin et al., 2020). Mutant TP53 reactivators have been developed which have been examined in certain cancer types, especially myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) patients with mutant *TP53* (Sallman et al., 2021; Cluzeau et al., 2021). Mutant TP53 reactivators have also been examined on PDAC cells (McCubrey et al., 2022b).

Mouse double minute 2 (MDM2) is a ubiquitin ligase which will target the TP53 protein for proteasomal degradation which results in destabilization of TP53 protein. MDM2 inhibitors result in the stabilization of the TP53 protein and have been examined in clinical trials with certain cancer types (Tisato et al., 2017; Konopleva et al., 2020; Shen et al., 2021). MDM2 inhibitors could synergize with topoisomerase II inhibitors such as etoposide to induce TP53-independent death in PDAC cells in vitro (Conradt et al., 2013). MDM2 inhibitors will induce the genetic reprogramming of pancreatic stellate cells which in turn alters the hostile PDAC

microenvironment and suppresses PDAC progression (Saison-Ridinger et al., 2017). There are twenty-seven listed clinical trials with MDM2 inhibitors and cancer patients. One clinical trial will be performed with pancreatic cancer patients.

Recently the combination of treatment cells with chloroquine and MEK inhibitors have shown promise in treatment of *KRAS*-mutant PDAC cells (Bryant et al., 2019; Kinsey et al., 2019). Additional studies have shown that combinations of ERK and IGF-1R inhibitors will synergize with chloroquine and inhibit the proliferation of PDAC in cell lines and tumor models in mice xenografts (Stalnecker et al., 2022).

Chloroquine also potentiates the effects of PI3K/Akt inhibitors in triple negative breast cancer (TNBC) cells and overcomes the resistance that these cells have to PI3K/Akt inhibitor (Cocco et al., 2022). TNBC is a difficult breast cancer to effectively treat. In the above study it was demonstrated that chloroquine in combination with the chemotherapeutic drug paclitaxel could overcome the resistance of the TNBC to PI3K/Akt inhibitors. PI3K/Akt inhibitors can induce autophagy in TNBC cells, which results in drug resistance. In contrast, chloroquine can repress the induction of autophagy in TNBC cells, and this led to sensitization of the breast cancer cells to PI3K/Akt inhibitors and paclitaxel.

Chloroquine also has effects on the TP53 protein. TP53 can activate AMP-activated protein kinase (AMPK) and tuberous sclerosis proteins 1 and 2 (TSC1/TSC2) and inhibition of mechanistic target of rapamycin complex 1 (mTORC1) (Kondo and Kondo., 2006) which promotes autophagy. Chloroquine induced the stabilization of the TP53 protein in glioma cancer cells. This resulted in the induction of apoptosis. It also induced the transcription of the *TP53* gene (Kim et al., 2010). Chloroquine can have effects on various cancer cells in TP53-dependent and TP53-independent fashions (Kim et al., 2010; Geng et al., 2010; Liu et al., 2014). The potential of re-purposing chloroquine in cancer therapies has been proposed (Weyerhäuser et al., 2018). The effects of chloroquine have been examined in 23 clinical trials patients having with different types of cancer.

Chloroquine also has effects on the immune system in mouse models of melanoma and hepatocellular cancer (Chen et al., 2018). Chloroquine was observed to shift the presence of tumor associated macrophages (TAMs) of the M2 phenotype in M1 macrophages which are more tumoricidal. The M1 macrophages induced by chloroquine improved the tumor immune microenvironment The immunosuppressive infiltration of myeloid-derived suppressor cells and Treg cells were reduced, and improved ant-tumor was observed. Mechanistically, chloroquine was observed to induce the $p38^{MAPK}$ kinase and NF-κB transcription factor and some other regulatory molecules which stimulated the conversion of M2 into M1 macrophages.

Another key pathway which is involved in autophagy is the mTORC1 pathway. The mTORC1 pathway. mTORC1 is a suppressor of autophagy. mTORC1 inhibitors such as rapamycin and rapamycin analogues (rapamycin) induce autophagy (Kim and Guan, 2015). The effects of mTORC1 inhibitors have been examined in approximately 30 clinical trials with PDAC patients.

Chloroquine is different type of inhibitor as it suppresses a biochemical process as opposed to a single protein. Hydroxychloroquine is a derivative, and it is the more commonly used form of chloroquine now as it is more water soluble (Browning, 2014). It has been used in the treatment of multiple diseases. Chloroquine inhibits autophagy and can suppress cancer growth (Bryant 2019; Piffoux et al., 2021), although in some studies it has been shown that chloroquine can promote tumor growth. Chloroquine has been proposed as an anti-cancer drug (Manic et al., 2014; Zhang et al., 2015). A recent study indicated that palmitoyl-protein thioesterase 1 (PPT1) is a molecular target of chloroquine in cancer (Rebecca et al., 2019).

There have been approximately 102 studies with hydroxychloroquine and patients with various types of cancer. In this group of studies, 14 focused on PDAC. In one trial with hydroxychloroquine as the single agent, no improvement was observed in terms of survival in terms of untreated patients (Wolpin et al., 2014).

The effects of hydroxychloroquine and gemcitabine and nab-paclitaxel were determined in a clinical trial, the combination did not appear to improve the survival of PDAC patients at the 12-month survival point (Karasic et al., 2019). Previously, the effects of hydroxychloroquine and gemcitabine and nab-paclitaxel were determined in cells from gemcitabine and nab-paclitaxel treated PDAC patients and mouse orthotopic tumor studies. It was observed that hydroxychloroquine reduced the formation of neutrophil extracellular traps and hypercoagulability (Boone et al., 2018). The effects hydroxychloroquine and gemcitabine and nab-paclitaxel have been examined in approximately five other clinical trials.

Both the MEK1 and ERK1,2 enzymes lay downstream of KRas which is frequently mutated in PDAC. The effects of hydroxychloroquine and MEK1 or ERK1,2 inhibitors in PDAC patients are being examined in approximately four clinical trials.

There are many other concepts that are being investigated in PDAC in combination with hydroxychloroquine. One clinical trial will examine the effects of radiation and capecitabine (capecitabine is metabolized to 5-FU which has been used for decades in the treatment of PDAC patients). Another clinical trial will examine the effects of folfirinox and chlorpensin carbamate (a muscle relaxant). The effects of a vitamin D analogue paricalcitol and either gemcitabine and nab-paclitaxel in one clinical trial. The effects of paricalcitol, losartan (an angiotensin II receptor II blocker), nab-paclitaxel, gemcitabine and cisplatin are being examined in another clinical trial with hydroxychloroquine. Obviously, many different approaches are being examined as attempts to treat PDAC patients.

2. Discussion

There are few effective therapies for PDAC which remains one of the deadliest cancers. PDAC is frequently diagnosed late in the course of the disease progression which makes effective therapy difficult to near impossible. Unfortunately, the expression of many genes is altered in PDAC. Two of the most common mutations in PDAC are the *TP53* and *KRAS* genes. Effective targeting of these proteins encoded genes has proven difficult and they were

considered undruggable proteins. Recently, novel KRas inhibitors have been developed as well as compounds which will reactivate mutant TP53 and are being evaluated in the treatment of certain cancers (Canon et al., 2019; Hallin et al., 2020; Hong et al., 2020; Sallman et al., 2021). The KRas inhibitors and the mutant TP53 reactivators are in clinical trials with colon cancer and leukemia patients respectively, but not currently in clinical trials with PDAC patients.

Although the effects of chloroquine and hydroxychloroquine have been more established on diseases such as malaria, chloroquine and hydroxychloroquine are now being repurposed as anticancer drugs (De Lellis et al., 2021). Chloroquine can inhibit autophagy which is important in cancer survival in the hostile tumor microenvironment. Recent studies suggest that the anti-cancer effects of chloroquine and hydroxychloroquine maybe increased in certain cancers by the co-addition of inhibitors which target signal transduction proteins such as MEK, ERK, BRAF and IGF-1R.

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Declaration of competing interest

The authors declare that they have no conflict of interest with publication of this manuscript.

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Table 1. Clinical Trials with Pancreatic Cancer Patients (Total listed 1562)[1]							
Chemotherapy (N = 1192)		Other Therapeutic Approaches (N = 1512)		Targeted Therapy (N = 397)		Repurposing of other drugs/vitamins (N = 78)	
Drug	# of Trials	Therapeutic approach	# of Trials	Target	# of Trials	Drug/vitamin	# of Trials
Gemcitabine	925	Surgical Resection		PARP	40	Metformin	23
Nab-paclitaxel	338	Surgery	618	mTORC1	33	Vitamin C	19
Oxaliplatin	286	Radiotherapy		MET	23	Vitamin D	19
5-Fluorouracil	272	Radiation	574	EGFR	21	Statins	6
Cisplatin	102	Photodynamic Therapy		MEK	17	Fish Oil	4
Docetaxel	47	Photodynamic	6	COX2	15	Curcumin	4
Doxorubicin	19	Immunotherapy		VEGFR1	15	Aspirin	3
Temozolomide	18	Various MoAbs	179	Proteasome	9		
5-Azacytidine	7	Checkpoint Inhibitors	91	Ras	7		
Etoposide	6	CAR-T Cells	44	PI3K	7		
Daunorubicin	1			BRAF	7		
				Hedgehog	6		
				NOTCH	4		
				FGFR	3		
				AMPK	3		
				GSK-3	3		
				Akt	2		

[1]Data obtained from clinicaltrials.gov as of September 19, 2022.