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Immunosuppressive Effects of Capecitabine Chemotherapy and Protective Effects of Vitamin C

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Abstract

Review Article

Chemotherapy drugs can have different immunosuppressive effects and specifically reduce the number of white blood cells such as lymphocytes and leukocytes. Capecitabine is a new well-tolerated chemotherapy agent that is effective in treating certain cancers, especially breast cancer and gastrointestinal cancers such as colorectal, gastric and pancreatic cancers. Similar to other chemotherapeutics, capecitabine causes the formation of excess reactive oxygen species and a decrease in plasma antioxidant levels. It has been reported that capecitabine causes immune suppression and lymphopenia in cancer patients. Vitamin C, a well-known chelating agent with non-enzymatic antioxidant properties, repairs oxidative damage by reducing lipid peroxidation, altering the antioxidant defense system, showing electrons to free radicals, and extinguishing the reactivity of free radicals. These properties of vitamin C can provide very beneficial effects against organ damage. Vitamin C has been found to be beneficial for improving liver damage. Using vitamin C as an adjunct to minimize the toxic side effects of capecitabine can be helpful.

INTRODUCTION

Chemotherapy is one of the commonly used interventions for cancer treatment [1]. Despite the availability of new chemotherapeutic drugs and advances in radiation therapy, traditional cancer therapy often fails to control the progression of the tumor [2]. In some cases, chemotherapy drugs cannot be successful due to pharmacokinetic and pharmacodynamic properties, such as the development of drug resistance in cancer patients and the insufficient concentration of the drug passing into the tumor [3]. The cytotoxic effect of cancer chemotherapy is not selective for cancer cells, it also affects normal tissues [1]. The amount and severity of chemotherapy damage to healthy tissues depends on the type, amount and duration of the drug used [4].

Chemotherapy drugs can be divided into several categories based on factors such as the way they work, their chemical structure and their interactions with other drugs [1]. The most important categories are alkylating agents (such as cyclophosphamide, ifosfamide, melphalan, busulfan), antimetabolites (such as 5-fluorouracil, capecitabine, methotrexate, gemcitabine), antitumor antibiotics (such as daunorubicin, doxorubicin, epirubicin), topoisomerase inhibitors (such as topotecan, irinotecan, etoposide, teniposide) and mitotic inhibitors (such as paclitaxel, docetaxel, vinblastin, vincristine) [5].

All chemotherapeutic agents have a toxic effect on target cells. The kinetics of this effect depends on the dose of the drug [2]. Many chemotherapeutic drugs target the cell cycle, thereby affecting cancer clones where cell division is common rather than normal cells. During this process, slow-growing cancer clones remain viable and become new fast-growing strains [1]. Chemotherapy kills most sensitive tumor cells and manages to keep the patient in remission for weeks or months after the tumor reappears as a more aggressive organism [6].

Many anticancer drugs cause DNA damage to promote apoptosis in cancer cells [7]. There are many studies showing that apoptosis is stimulated by reactive oxygen species that are created directly or indirectly by anticancer drugs [8]. Death factors known to promote apoptosis are tumor necrosis factor-α (TNF-α), fas ligand, lymphotoxin α, TRAIL/Apo2 ligand and Apo3 ligand. Chemokines promote positive chemotaxis in blood cells that synthesize these death factors. For example, neutrophils producing the fas ligand migrate to the dermis in response to chemokines produced by keratinocytes. These neutrophils undergo apoptosis in response to reactive oxygen species. At the same time, caspase-1 in neutrophils is activated and interleukin-1β (IL-1β) is released from neutrophils. Cells

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exposed to apoptosis do not promote inflammation. They are absorbed by phagocytes or surrounding cells [7].

Immune suppressive effects of chemotherapy

Many studies report that chemotherapy drugs can have different immunosuppressive effects and reduce the number of white blood cells, specifically lymphocytes and leukocytes [1, 2, 9]. In a study [10], 3 or 4 degree lymphopenia was observed in 258 breast cancer patients after the 5th cycle of chemotherapy. In another study [11], it was observed that antibodies formed against measles and rubella disease were lost in children treated with intensive chemotherapy. Again, chemotherapy inhibited antigen-specific T lymphocyte cells resulting from cancer vaccines previously given in patients receiving combined therapy [12]. In another study, T lymphocyte counts decreased significantly after chemotherapy and radiotherapy treatment of 34 patients with breast cancer [13].

Chemotherapy and pro-inflammatory cytokines

The discovery of TNF, a serum protein that can cause hemorrhagic necrosis of the tumor in mice in 1975, has led to an increase in research aimed at utilizing its potent anti-tumor activity in cancer patients. Unfortunately, despite the impressive anti-tumor effects observed in animal models of TNF, in phase I and phase II clinical trials several years later, it caused toxic effects when administered systemically to patients and either did not stimulate anti-tumor responses or warned at very low levels [14]. Therefore, various studies have been planned by combining TNF with other drugs or cytokines, changing the circulating half-life of TNF, or preparing less toxic TNF mutants [15]. TNF can increase endothelial permeability and reduce the pressure of intercellular fluid in tumors in order to allow rapid penetration of the chemotherapy drug. Thus, convective transport of chemotherapy drugs through interstitium and the walls of the tumor vessel, and as a result, drug uptake by tumor cells can be increased [16]. Bunt et al. [17] found that pro-inflammatory cytokines IL-6, monocyte chemoattractant protein-1 (MCP-1), transforming growth factor -β (TGF-β) and IL-1β were significantly increased in breast tumor tissue, and reported that this indicates that tumor growth is associated with an inflammatory environment.

There is evidence that interferon-ɣ (IFNɣ) produced by tumor-infiltrating macrophages plays a role in the destruction of the blood vessels of the tumor [18]. IFNɣ can also inhibit tumor vascularization and increase the synthesis of major histocompatibility complex-I (MHC-I) and MHC-II in cancer or endothelial cells. Also, IFNɣ can induce secretion of cytokines and chemokines, such as an angiostatic protein in the tumor stroma and an IFNɣ-induced protein-10 that is a chemoattractant factor for lymphocytes and monocytes [19]. Combined treatment of endothelial cells with IFNɣ and TNF can cause synergistic cytotoxic effects that are important for tumor vessel destruction. In addition, IFNɣ promotes anti-proliferative and pro-apoptotic effects on many tumor cell types and activates natural killer cells and macrophages to kill tumor cells [18]. IFNɣ is also an important regulator of T lymphocyte helper cells. As a result of these effects on tumor vascularization and immune system cells, IFNɣ can activate inflammatory/immune responses against tumors that occur and inhibit tumor growth [16]. Due to its immunomodulatory and anti -cancer activities, IFNɣ has been used as an anticancer drug in several clinical studies, but unfortunately, moderate results have been obtained [20].

The use of biomarkers to determine the severity and course of damage associated with cancer therapy is not new [21]. For this purpose, some biomarkers, such as citrulline, calprotectin and proinflammatory cytokines, have been investigated. It has been claimed that apoptotic and inflammatory markers that can be detected in cytological smears are strong markers of oral mucositis. The elevated levels of pro-inflammatory cytokines, especially TNF, IL-1β and IL-6, were found to be excellent markers of the inflammatory response caused by chemotherapy, and TNF, IL-1β and IL-6 were associated with the formation of gastrointestinal mucositis caused by chemotherapy [22]. In a study, TNF, IL-1β, matrix metalloproteinase-3 (MMP-3) and MMP-9 were reported to be strong biomarkers of gastrointestinal toxicity caused by 5-fluorouracil, capecitabine or irinotecan [21]. In another study, gene expression and tissue levels of TNF-α and IL-1β were shown to be closely correlated with mouth and intestinal mucosa damage following radiation [23].

What is Capecitabine?

Capecitabine (N4-pentyloxycarbonyl-5'-desoxy-5-fluorositidine) is a new well-tolerated chemotherapy agent that is effective in the treatment of breast cancer and gastrointestinal cancers such as colorectal, gastric and pancreatic cancers

(Figure 1) [9]. Capecitabine, which is the precursor of 5-fluorouracil with high tumor selectivity, is used orally. It is also thought that capecitabine is the standard treatment option in advanced colorectal cancer and an adjunct therapy in colon cancer [1].

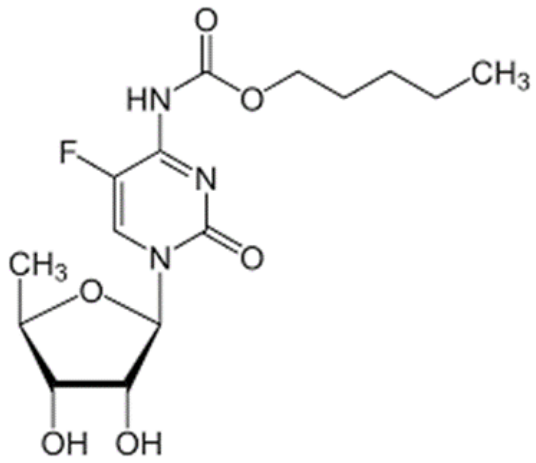
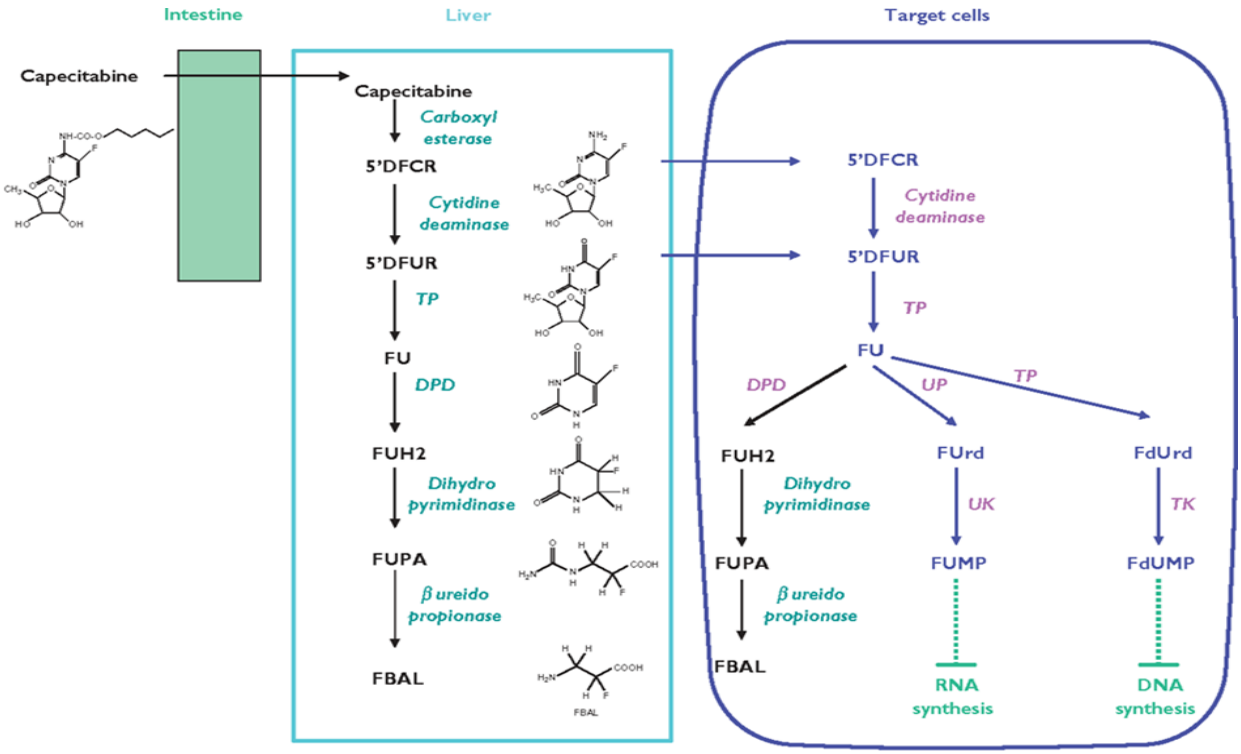


Figure 1: The formula of capecitabine (https://en.wikipedia.org/wiki/Capecitabine)

Metabolism of Capecitabine

Capecitabine treatment results in 5-fluorouracil synthesis in tumor cells [24]. Capecitabine is converted into fluorouracil through an enzymatic cascade of 3 steps, mostly in tumor tissue, and also in the liver [1]. In the first step, capecitabine is hydrolyzed in the liver to 5'-deoxy-5-fluorositidine by a hepatic enzyme, carboxyl esterase. In the second step, 5'-deoxy-5-fluorositidine is converted to 5'-deoxy-5-fluorouridine by the citidine deaminase enzyme, which is highly active in liver and tumor tissue (Figure 2). 5'-deoxy-5-fluorouridine is the precursor of 5-fluorouracil and is taken up by solid tumors after endogenous synthesis in patients treated with capecitabine. Plasma membrane carriers regulate the uptake of 5'-deoxy-5-fluorouridine into tumor cells. In this case, the efficacy of capecitabine depends not only on the activities of the enzymes, but also on the transport process. The synthesis of the specific carrier protein increases the sensitivity to capecitabine. The human concentrative nucleoside carrier (hCNT1) is the carrier of 5'-deoxy-5-fluorouridine and its synthesis shows drug sensitivity [24].



5'DFCR = 5'deoxyfluorocytidine
5'DFUR = 5'deoxyfluorouridine
FUH2 = dihydrofluorouracil
FUPA = α-fluoro-β-ureidopropionate
FBAL = α-fluoro-β-alanine
FURd = fluorouridine
FUMP = fluorouridine monophosphate
TK = thymidine kinase
TP = thymidine phosphorylase
UP = uridine phosphorylase

Figure 2: Metabolic pathways of capecitabine [26]

In the third step, 5'-deoxy-5-fluorouridine is converted into cytotoxic 5-fluorouracil by the thymidine phosphorylase enzyme in tumor tissue (Figure 2). Thymidine phosphorylase is synthesized at levels 3-10 times higher in tumor cells than in healthy tissues [25]. Various tumor tissues may contain different levels of thymidine phosphorylase enzyme activity. This enzyme can also limit the production of 5-fluorouracil [24]. Thymidine phosphorylase then activates the conversion of 5-fluorouracil into fluorodeoxyuridine. Fluorodeoxyuridine inhibits DNA synthesis pathway in the tumor cell [26]. 5-fluorouracil is catabolized to dihydrofluorouracil by the enzyme dihydropyrimidine dehydrogenase, which is present in almost all tissues but is mainly found in the liver [26], and this reduced compound is then divided into ammonia, urea, carbon dioxide, and the α-fluoro-β-alanine which cause hepatotoxicity [1]. The main determinant of 5-fluorouracil-related toxicity is dihydropyrimidine dehydrogenase, the rate-limiting enzyme of 5-fluorouracil catabolism and which is responsible for 80-90% of the drug's clearance. Theoretically, the increased level of dihydropyrimidine dehydrogenase should increase the production of 5-fluorouracil catabolites, namely dihydrofluorouracil and α-fluoro-β-alanine [26, 27]. When 5-fluorouracil is given intravenously for the treatment of breast and gastrointestinal cancers, it is metabolised to fluorodeoxyuridine monophosphate, which is the active form in the tissues and inhibits thymidilate synthase enzyme [1].

Immunosuppressive effects of Capecitabine

Similar to other chemotherapeutics, capecitabine causes the formation of excess reactive oxygen species and a decrease in plasma antioxidant levels. This reduction reflects the inadequacy of the antioxidant defense mechanism against oxidative damage [1]. In a study, 5-fluorouracil significantly reduced the percentage of myeloid-derived suppressor cells [28]. Preclinical data prove that the reduction of myeloid-derived suppressor cells increases the effectiveness of cancer immunotherapy [24]. The effect of 5-fluorouracil suppressing tumor growth depends on the presence of T lymphocyte cells [28].

It has also been reported that capecitabine causes immune suppression and lymphopenia in cancer patients [9]. In a study, 30.5% lymphocytopenia was observed in patients with advanced metastatic colorectal cancer following capecitabine treatment [29]. In another study [30], 3rd and 4th degree leukopenia was found in 66% of patients with metastatic breast cancer following the combined treatment of capecitabine-docetaxel.

Combined therapy of bevacizumab, capecitabine, and gemcitabine applied to patients with advanced pancreatic cancer has been reported to cause 3rd degree neutropenia in 22% of patients [31]. In another study where oral vinorelbine and capecitabine was administered to patients with metastatic breast cancer, 49% of patients developed 3rd and 4th degree neutropenia [32]. The addition of interferon-α to low-dose capecitabine increased survival rates by providing inflammation control [33]. Fujimoto-Ouchi et al. [34] proved that capecitabine reduced plasma IL-6 levels in patients with cachectic cancer.

Side effects of Capecitabine

One of the main handicaps of the current treatment methods of cancer are possible side effects of treatment methods [1]. Capecitabine is generally a well-tolerated chemotherapeutic. The most common dose-limiting side effects of capecitabine are diarrhea, hyperbilirubinemia, and hand-foot syndrome, also called palmar-plantar erythrodysesthesia [26]. Due to the reactive oxygen species formed as a result of capecitabine treatment, keratinocytes, blood cells and fibroblasts produce inflammatory cytokines such as IL-1β that cause vasodilatation, skin redness, fever, increased vascular permeability and swelling, that is, hand-foot syndrome [7, 35]. The overall incidence of hand-foot syndrome observed with capecitabine in clinical trials of breast and colorectal cancer was found to be around 50%. 17% of this was patients who showed the 3rd degree, the serious form [36]. In one study, capecitabine compared to the 5-fluorouracil/ leucovorin mixture caused more hand-foot syndrome but less stomatitis, alopecia, diarrhea, nausea and neutropenia [37].

Capecitabine itself is not toxic, but after converting it to fluorouracil in tumor cells, it begins to show a toxic effect [1]. Deficiencies in dihydropyrimidine dehydrogenase, the enzyme responsible for catabolizing 5-fluorouracil in the liver, also led to increased toxicity [21]. Rats treated with capecitabine have shown varying degrees of clinical findings in studies. These findings were in form of gathering of animals, conjunctivitis, mild tremor, piloerection and myelosuppression [1]. Other common side effects include fatigue, weakness, abdominal pain, and gastrointestinal effects such as nausea/vomiting, stomatitis/mucositis and diarrhea [26]. Conversion of capecitabine to 5'-deoxy-5-fluorositidine, a cytotoxic agent in the gut, may

be responsible for gastrointestinal side effects [1].

Olayinka et al. [38] reported that capecitabine caused liver damage. There was also a loss of liver and body weight. Decreased body weight can result from decreased skeletal muscles and adipose tissue. Also, the decrease in body weight of the animals may be due to the decrease in feed consumption [1].

Protective effects of vitamin C

Vitamin C is the most important free radical scavenger in extracellular fluids, which captures free radicals which can also occur during normal metabolism, other than those formed due to toxins and carcinogens, and protects biological membranes from peroxidative damage. Vitamin C, a well-known chelating agent with non-enzymatic antioxidant properties, repairs oxidative damage by reducing lipid peroxidation, altering the antioxidant defense system, showing electrons to free radicals, and extinguishing the reactivity of free radicals [39]. These properties of vitamin C are thought to provide very beneficial effects against organ damage [1].

Using vitamin C as an adjunct to minimize the toxic side effects of capecitabine can be helpful. For example, it has been found that vitamin C is useful for improving liver damage. Treatment of rats with capecitabine has caused many histological changes, such as leukocyte infiltration, in addition to blood vessel congestion and necrosis in the liver. Treatment with vitamin C reduced the hepatotoxic properties of capecitabine in the rat liver, which showed that vitamin C protects against capecitabine-induced liver damage [1].

Glutathione acts as an intracellular free radical scavenger and protects cells against lipid peroxidation mediated by free radicals. Vitamin C also prevented depletion of hepatic glutathione in chemically induced hepatotoxicity in mice [40]. In a study, vitamin C reduced kidney failure caused by oxidative stress [41]. The addition of vitamin C improved acute kidney failure caused by cisplatin in mice and protected cells against lipid peroxidation caused by free radicals [40]. Atasayan et al. [42] reported that the combined treatment of cisplatin, vitamin C and vitamin E can improve histopathological changes caused by cisplatin on the kidney, compared to the group treated with a single acute toxic dose (7.5 mg/kg) of cisplatin.

Similar to all other chemotherapy drugs, capecitabine can cause immune suppression and some side effects. However, it is a chemotherapeutic agent that is generally well tolerated. Since vitamin C is a good antioxidant, it may benefit against unwanted side effects such as liver damage caused by capecitabine.

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