Review Article

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A Review of Some Treatments for Oral Mucositis Induced by Using 5-Fluorouracil

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Abstract
Oral mucositis (OM) remain the principal complication and costly side effect of cancer chemotherapy. It is creating progressively important contribution to mortality rate as the clinical manifestation ranging from moderate including pain and impairs food and drink ingestion to sever mucosal lesion which developed to life threading due to intense immune suppression. 5-Fluorouracil (5-FU) is a pyrimidine analogue which considered as a vital treatment for diversified shapes of solid tumors for over 40 years. Intravenous (IV) route of 5-Fluorouracil medication treating are commonly used. Experimental studies had demonstrated that the uracil was necessary for sustaining nucleic acid synthesis required for tumor growth, this led to hypothesis the 5-flurauracil might interfere with nucleic acid synthesis and slow tumor growth. Use of 5-FU drug is one of the most common causes of OM. Our review demonstrates and cooperate the drugs and beside diminish riskiness of chemotherapy 5-FU as a causes of OM in experimental animal.

Keywords: Oral mucositis, 5-Fluorouracil, Chemotherapy, Experimental, Immune suppression.

Introduction

OM is defined as an inflammatory response of the oral mucosa with complex patho-physiology and multifactorial [1]. Mucositis lesions screening revealed thinning of mucosal layer due to apoptosis and epithelial basal layer depletion, and subsequent to secondary bacterial infection [2]. OM lead to the oxidative stress and reactive oxygen species [3] Oxidative stress can lead to lipid peroxidation and inflammation [4]. The resulting inflammation causes ulceration and development of inflammatory cytokine-mediated damage which is exacerbated by bacterial colonization, feeding a vicious cycle of inflammatory cytokine-mediated harm. [5].

Mucositis may occur with 5-FU a nucleoside metabolic inhibitor indicated for

the treatment of patients with adenocarcinoma of the colon and rectum.
- Pancreatic Adenocarcinoma.
- Adenocarcinoma of the Breast.
- Gastric Adenocarcinoma.

5-flurauracil created about 40 years ago and became as a preferred anticancer medicine for treatment of various types of malignancies alone or by using it with other drugs.

It has an anodyne action on breast, gastrointestinal, ovary cancer and therapeutic effect on basal cell carcinoma.

In 1950s, studies assigned that uracil was taken up and joined to a much greater range in cancer tissues in comparison with health tissues, The manufacturing of uracil analogs of which 5-FU was the most vigorous towards cancer models in rodents (6).

5-Fluorouracil work by suppression of DNA synthesis this indistinctive action mechanic affects the normal dividing cells in addition to tumor cells. The high proliferative efficacy in gastrointestinal tract makes it a highly susceptible to the harmful side-effects of chemotherapy medicine, leading to a state called mucositis (7).

Induce a model of oral mucositis

In different experimental animals models for chemotherapy-induced oral mucositis was instituted on a modulation of the style of previous study (8). To enhance OM, the mucosa of the cheek pouch was irritated by superficial scratching. To mimic the clinical indications of persistent irritation and develop a condition, the tip of an 18-gauge needle was dragged across the averted cheek pouch in a linear way twice favorable for OM similar to human OM by mechanical trauma (MT). 5-FU injection comes in a vial containing 5% in a pharmacy bulk container. The occurrence of OM is declared to be higher with IV bolus compared with continuous infusion. Intra peritoneal injections of 5-FU (60mg/kg) withhold is recommended in the experimental animals (rabbits, hamsters, rats, monkeys) to induce OM .

Chemical structure of 5-FU:

5- FU is an analog of uracil with a fluorine atom at the C-5 location in place of hydrogen (fig.1), the Vander Waals radius of the atom likes that of hydrogen which permits the molecule to imitate uracil biochemically (9). 5-FU quickly gets in the cell employing the similar facilitated transportation method as uracil and intracellular submits to the same anabolic and catabolic responses like uracil , with the exemption of the methylation at location 5, stimulated by thymidylate synthase (TS), it is most significant goal of 5-FU in tumor cells.

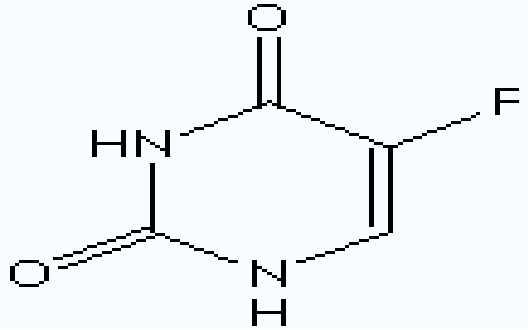

Figure1: Chemical structure of 5-FU

Pathogenesis of oral mucositis caused by 5-FU:

OM predominantly occurs of human patients treated by chemotherapeutic agent as a usual example of these drugs is 5-FU (10). The signs of OM are maceration, with severe ulceration and inflammation affecting the mouth (11). The modern

medicines are directed to overcome and alleviation of extra defect, by describing the keratinocyte growth factor, cryotherapy and anti-inflammatory drugs but with unsuccessful improvement because of their inconstant efficacy (12) therefore, there is obvious necessity for the development of treatment technique.

Methods used for treatment of 5-fu induced om

● **Odara** *et al*., (2013) evaluate the glycine supplementation reducing effect on the 5-FU induced OM in an animal model hamster by reducing the production of harmful free radicals and inhibiting the inflammatory response. Glycine (Ajinomoto, Raleigh, NC) diluted in saline was administered intra-peritoneal to animals at a rate of 2 mg/g body weight at a concentration of 5%. Administration is applied a one time during a day (morning), for 7 days. It has been found that glycine administration able to reduce chemotherapy related injury. Glycine has positive effects against the pathogenesis of OM induced with 5-FU, as well as the effects of systemic glycine supplementation against intensity OM (13, 14).

● **Aurigena** *et al*., (2015) an experimental model was used to test the anti-inflammatory effects of the angiotensin receptor blocker azilsartan (AZT) of OM . Three dosage of AZT 1, 5, and 10 mg/kg used. Hamster treated with oral administration of azilsartan revealed diminutive cellular inflammation, edema, and hemorrhage, In addition, presence of granulation tissue and moderate extent for the macroscopic and histologic scores was cleared with examination. The clinical data of this research has been found that AZT expedites the recovery mode in a hamster pattern of 5-FU induced OM, through promoting the production of granulation tissue, the migration of fibroblasts and keratinocytes, and the deposition of collagen. These data were curtained with highest TGF-α, FGF, and KGF levels, and up arranging of VEGF, revealed enhance angiogenesis in scar tissue (15, 16).

● **Anaet** *et al*., (2012) studied anti-inflammatory effect of Calotropis procera latexon on 5-FU induced OM. *Calotropis procera* is a laticiferous plant (Apocynaceae) The latex ingredients of *C. procera* as a laticifer proteins appear to induce interesting biological effects, and pharmacological properties of whole plant. Four doses of laticifer protein of *C. procera* applied (0.25, 1, 5, and 25 mg/kg) 24 h before and 24 h after cheek pouch abrasion. This experiment has effectively demonstrated that laticiferous proteins have many of a hopeful goods to protect animals against experimentally induced lethal sepsis (The protective mechanism of LP due to suppression of the expression of iNOS, COX-2, TNF-α, and IL-1β (17, 18).

● **Mutan** *et al*., (2013) scientifically evaluate the beneficial effect of boron contents in treated OM formed by the chemotherapeutic 5-FU medicine in a rat. Boron known as a mineral that is a plentiful in soil, air, and the most prominent boron components are boric acid and borax. Animals with boron treated group were fed a powder form (3mg/kg) once a day. Histological sections show graduated healing of inflammation process according to period of treatment and in the

late stage of boron administration Re-epithelization was complete. It has been that boron reduces oxidative damage by speeding up the body's production of glutathione and its derivatives, as well as providing immediate ROS-neutralizing agents (19).

● **Najmeh** *et al*., (2016) showed topical application of olive leaf extract ointment on oral lesion produced by 5-FU in golden hamsters and diagnosis by clinical, histology, and serum biochemical estimate. For 5 days, animals were given a topical application of ointment (Zaitonex, which contains 0.45% oleuropeine (OLE) or a base of ointment. Because of its antioxidant and anti-inflammatory properties, daily administration of OLE ointment was effective in the treatment of OM, according to the findings. Histopathologic screening olive leaf extract reduced Lesions scores of OM. This confirmed that OLE could reduce inflammatory responses related to 5-FU-induced mucositis. In addition OLE has effective mechanism by increased collagen concentration and fibers' stabilization as a part of wound healing effect (20, 21, and 22).

● **Ha-Reum** *et al*., (2016) PLAG (1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol) has been shown to improve recovery from 5-FU-induced OM and inhibit inflammatory responses in the tongue and serum. PLAG (*Enzychem Lifesciences*) was given orally at 250 mg/kg/day beginning on day 7 of OM induction. Resulting data assigned that PLAG increase healing state of 5-FU-induced OM and consider as a helpful medicinal factor for treating toxic effects of anticancer drugs, including mucositis and cachexia (weight loss). Histochemical staining data revealed that PLAG has a newly differentiated epidermis and blood vessels in PLAG-treated hamsters. Total blood test confirmed that PLAG blocks 5-FU-induced extra neutrophil transmigration and establish the circulating neutrophils levels (23, 24).

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مراجعة لبعض علاجات التهاب الغشاء المخاطي الفموي المستحدث بأستخدام ال 5- فلورويوراسيل

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الخلاصة

يعد التهاب الغشاء المخاطي الفموي من المضاعفات الرئيسية والاثار الجانبية المكلفة للعلاج الكيميائي للسرطان، اذ انه يساهم بشكل متزايد في معدل الوفيات ، وان العلامات السريرية للالتهاب تتراوح من معتدلة تشمل الالم وقلة في تناول الطعام والشراب الى الافة المخاطية الشديدة التي من الممكن ان تتطور الى تعفن الدم الخيطي نتيجة للتثبيط المناعي الشديد.

يعتبر ال5- فلورويوراسيل من نظائر البريمدين والتي عرفت كجزء من مجموعة لعلاج انواع من الاورام الصلبة لاكثر من أربعين سنة. يتطلب العلاج بال 5- فلورويوراسيل أعطاءه عن طريق الحقن بالوريد بسبب سوء التوافر الحيوي عند اعطاءه عن طريق الفم وكذلك عدم انتظامه.

وقد اظهرت الدراسات التجريبية ان اليوراسيل ضروري للحفاظ على تخليق الحمض النووي المطلوب لنمو الورم مما قاد الى فرضية قدرة ال5- فلورويوراسيل القدرة على التداخل في تخليق الحمض النووي وابطاء نمو الورم.

استخدام ال5- فلورويوراسيل كعلاج هو احد اسباب الالتهاب المخاطي الفموي الذي يؤدي الى تاخر، وتقليل الجرعة الدوائية ،او حتى ايقاف العلاج للورم في اكثر من 15% من الحالات المعالجة بال 5- فلورويوراسيل.

الدراسة الحالية توضح وتقارن بين بعض العلاجات والمكملات التي تقلل من شدة الالتهاب المخاطي الفموي الناجم عن العلاج الكيميائي ال5-فلورويوراسيل باستخدام نماذج حيوانية.