A Research Proposal for Partial Fulfillment of Master Degree of Pharmacy (Clinical Pharmacy)

Proposal Title

The Possible Protective Effect of Pentoxifylline against Chemotherapy Induced Toxicities in Patients with Colorectal Cancer

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in recent years, and the second leading cause of cancer death globally. In 2020, CRC accounts for 10% of global cancer incidence and 9.4% of cancer deaths, just lower than lung cancer. The global number of new CRC cases is predicted to reach 3.2 million in 2040 (**1, 2**).

Oxaliplatin is a third-generation platinum-based chemotherapy drug that is considered a key drug in treatment of colorectal cancer (**3**).The most reported adverse effect of oxaliplatin is neurotoxicity. Oxaliplatin induces two forms of peripheral sensory neuropathy. The first is transient, acute neuropathy usually resolves spontaneously within days. The second form is chronic cumulative poorly reversible peripheral neuropathy that worsens with the repetition of chemotherapy cycles (**4**).

Although a number of interventions have been implicated, none of them can be recommended for clinical use (**5**). This therapeutic failure reflects poor understanding of the real mechanism of oxaliplatin-induced neuropathy (**6**). However, oxidative stress is identified to be one of the main bio-molecular dysfunctions in this neuropathy (**7**).

This oxidative stress can trigger inflammatory reaction which in turn up-regulates the expression of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which has been well demonstrated to play an important role in the establishment and maintenance of the spinal cord sensitization, resulting in hyperalgesia, and finally inducing neuropathic pain (**8**). Neurotensin (NT) is an endogenous neuropeptide involved in modulation of pain signal transmission and perception (**9, 10**). There is a significant increase in NT level in rats treated with oxaliplatin (**11**).

Intestinal mucositis, or damage to the intestinal mucosa, is a major contributor to the reduced quality of life, decreased survival rates, and early onset of death observed in patients with certain chemotherapeutic agents (**12**). Citrulline is an amino acid mainly produced by enterocytes of the small bowel. Decreased levels of plasma citrulline are correlated with significant epithelial small bowel loss (**13**).

Pentoxifylline (PTX), a xanthine derivative, has been shown to have a marked effect on cellular mediators of inflammation and tissue injury. It has been shown to inhibit TNF-α production, possibly via inhibition of TNFα and IL-1 mRNA transcription with relative preservation or even an increase of IL-10, an anti-inflammatory cytokine (**14, 15**).

Aim of the work

This study aims to:

- Evaluate the possible protective effect of pentoxifylline against oxaliplatin induced peripheral neuropathy and chemotherapy induced mucositis in patients with stage II and stage III colorectal cancer.

Patients and Methods

- Study design and treatment protocol:

This study will be a randomized placebo controlled parallel study. Forty-eight eligible patients with stage II and stage III colorectal cancer will be scheduled to receive 12 cycles of folinic acid, flurouracil and oxaliplatin (FOLFOX6 regimen). Patients will be recruited from the Oncology Department, Tanta University Hospital, Tanta, Egypt. Staging will be done according to the American Joint Committee on Cancer 7th edition staging. The patients will be randomized using according to the days of hospital admission into two groups:
Group I (control group; n=24) which will receive 12 cycles of FOLFOX-6 regimen plus placebo tablets twice daily.

The chemotherapy cycles will be received every 2 weeks and will be as follows:
Day 1: Oxaliplatin 85 mg/m^2 intravenous infusion in 250-500 mL 5% dextrose solution and leucovorin 400 mg/m^2 intravenous infusion in 5% dextrose solution both were given over 120 minutes at the same time in separate bags using a Y-line access, followed by 5-fluorouracil 400 mg/m^2 intravenous bolus given over 2-4 minutes, followed by 5-fluorouracil 2400 mg/m2 intravenous infusion in 1000 mL 0.9% SodiumChloride solution as a 46-hour infusion.

Additionally, Intravenous 5-HT3 antagonist plus pantoprazole will be administered to all participants before each cycle as prophylactic therapy against chemotherapy induced nausea, vomiting and mucositis. Furthermore, all participants will be submitted to complete blood count analysis before each chemotherapy cycle.

Group II (Pentoxiphylline group; n=24) which will receive FOLFOX-6 regimen in addition to pentoxifylline 400 mg twice daily.

- Ethical approval:

The study will be performed in accordance with the ethical standards of Helsinki declaration in 1964 and its later amendments. The study will be approved by the Research Ethics Committee of Tanta University. The study will be registered as a clinical trial at ClinicalTrials.gov. All participants will be informed about the benefits and risks of the study. Any unexpected risks that will appear during the course of the research will be clarified to the participants and to the ethical committee on time. The data of the enrolled patients will be confidential. All enrolled patients will give their written informed consents. The study will be conducted between October 2022 and October 2024.

- Inclusion criteria:

- Patients with histologically confirmed diagnosis of stage II and stage III colorectal cancer.
- Patients who will be scheduled to receive FOLFOX-6 regimen.
- Patients with no contraindication to chemotherapy.
- Males and females aged ≥ 18 years old.
- Adequate baseline hematologic values (absolute neutrophilic count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L and hemoglobin level ≥ 10 g/dl).
- Patients with adequate renal function (serum creatinine < 1.5 mg/dL and Creatinine clearance (ClCr) > 45 mL/min).
- Patients with adequate liver function (serum bilirubin < 1.5 mg/dl).
- Patients with performance status < 2 according to Eastern Cooperative Oncology Group (ECOG) score.

- Exclusion Criteria:

- Children < 18 years old.
- Prior exposure to neurotoxic chemotherapy (oxaliplatin, cisplatin, vincristine, paclitaxel, docetaxel or Isoniazid) for at least 6 months prior the study treatment.
- Evidence of pre-existing peripheral neuropathy resulting from another reason (diabetes, brain tumor or brain trauma).
- Patients with diabetes and other conditions that predispose to neuropathy as hypothyroidism, autoimmune diseases or hepatitis C.
- History of known allergy to oxaliplatin or other platinum agents.

- Patients with other inflammatory diseases (rheumatoid arthritis and ulcerative colitis) or stressful conditions (obesity class 2 and 3, smoking).
- Concomitant use of multivitamins (vitamins E, C and A), tricyclic antidepressants or other neuro-protective medications (gabapentin, lamotrigine, carbamazepine and phenytoin, etc…).
- Concurrent active cancer originating from a primary site other than colon or rectum.
- Patients on blood thinning agents
- Pregnant and breastfeeding women

- Measurements

A. Demography, physical examination and anthropometric data

Demographic data collection (age), medication history taking, physical examination and measurement of weight and height with subsequent calculation of body mass index according the following formula: BMI= [Weight (kg) ÷Height^2 (m)] will be done**.** Body surface area [Square root (weight "kg" X height "cm")/3600] and cumulative doses of chemotherapy will be also determined.

B. Blood sample collection and biochemical assessment

Before starting the first chemotherapy cycle (baseline) and after the last chemotherapy cycle, 5 ml of venous blood will be withdrawn by antecubital venipuncture from each participant between 8:30 and 10:30 am into plain test tube and centrifuged at 3000 rpm for 10 min. The separated sera will be frozen at -80°C until analysis of the biological parameters which include:

- Malondialdehyde (MDA) as oxidative stress marker (colorimetery).
- Tumor necrosis factor alfa (TNF-α) as pro inflammatory marker (ELISA).
- Neurotensin (NT) as a potential marker for neuropathic pain (ELISA).
- Citrulline as a biomarker for mucositis (ELISA).

C. Assessment of Chemotherapy induced toxicities

I. Clinical assessment of oxaliplatin induced peripheral neuropathy

Clinical assessment of oxaliplatin induced neuropathy will be done through:

- The assessment of the severity of neuropathic pain through brief pain inventory short form "BPI-SF" worst item (**16**). Severity of neuropathic pain will be assessed at baseline and by the end of every two chemotherapy cycles.
- The implication of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 5, 2017) for grading of neuropathy (**17**) at baseline and by the end of every two chemotherapy cycles.
- The use of Neurotoxicity- 12 item questionnaire score (Ntx-12) from the validated Functional Assessment of Cancer Therapy/Gynecologic Oncology Group "FACT/GOG-Ntx-12" (**18**) at baseline and by the end of every two chemotherapy cycles).

II. Clinical assessment of chemotherapy induced mucositis

- Mucositis will be assessed at baseline and by the end of every two chemotherapy cycles through the use of common terminology criteria for adverse events "CTCAE, version 5.00, 2017" (**17**).

D. Assessment of participants' adherence, side effects and tolerability

Pentoxiphylline will be provided on biweekly basis and the participants' adherence will be assessed through counting the returned tablets. Participants will be followed-up by weekly telephone calls and direct meetings during chemotherapy cycles to assess their adherence and to report any drug related adverse effects. The adverse effects will be collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse events "NCI-CTCAE; version 5, 2017" (**17**). Participants will be considered non-adherent and excluded from the study if not consumed the provided tablets or lost the follow-up meeting at any time of intervention or changed regimen.

- The primary and secondary endpoints:

The primary endpoint is the percentage of patients with peripheral sensory neuropathy grade ≥ 2, the variation of 12-item neurotoxicity questionnaire (Ntx-12) total score and the variation in grades of mucositis. The secondary endpoint is the change in the serum concentrations of the measured biological markers.

- Sample size calculation:

According to the results of previous studies, the total number of subjects required to detect the effect of neuro-protective drugs in patients received neuro-toxic chemotherapy was 41 patients with 5% significance, 80% statistical power and an attrition of 15 % (**19, 20**). In this context, during the current study, a total sample size of 41 patients in both arms will be sufficient to detect the effect. Assuming that the attrition rate will be 15 %, the initial sample size will be 48 patients in both arms with 24 patients in each arm.

- Statistical analysis:

- The collected data will be tabulated using Microsoft® Office Excel, 2019 (Microsoft Corporation).
- The statistical analysis will be carried out using SPSS statistical package version 26.0 (IBM corporation software group, USA).
- Data will be tested for normality using Shapiro-Wilk test or Kolmogorov–Smirnov test.
- Parametric data will be analyzed using Paired and un-Paired *t*-test to compare the means within the same group and to compare the means of the two groups respectively.
- Non- Parametric data will be analyzed using Mann Whitney U test to compare the means within the same group and to compare the means between groups.
- Categorical data will be analyzed using Chi-Square test.
- Fisher's exact test will be used to analyses the reported adverse effects.
- Correlation between variables will be assessed using Pearson or Spearman correlation coefficient which appropriate.
- Data will be expressed as the mean ± SD, medians, range, number and percent as appropriate.
- The significance level will be set at $p \leq 0.05$.

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