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ORIGINAL ARTICLE

The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer. A randomized clinical trial

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KEYWORDS

Oral mucositis;
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Benzydamine hydrochloride (Benzydamine HCl);
Proinflammatory cytokine;
Tumor necrosis factor-α (TNF-α);
Interlukien-1 β (IL-1β)

Abstract *Background:* Oral mucositis is the most common side effects of chemotherapy of all cancer with intensive treatments regimen, and is the most common side effects of head and neck radiation therapy. For steam cell transplantation, its also regarded as the most debilitating side effects.

Aims of the study: The objectives of this study were to assess the effect of a mouth rinse containing olive leaf extract (OLE) in preventing severe oral mucositis in patients receiving chemotherapy, and to estimate its effect in decreasing pro-inflammatory cytokine production after chemotherapy.

Materials and methods: This study utilized a placebo-controlled, randomized, double-blind, and cross-over design. Twenty-five patients undergoing intensive chemotherapy were randomly assigned to receive a mouth wash containing OLE, benzydamine hydrochloride, or placebo in 3 different cycles of chemotherapy. Oral mucositis severity was assessed using the World Health Organization criteria and Oral Mycositis Assessment Scale. Patients were evaluated weekly until 15 days after chemotherapy for each cycle. Salivary levels of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) were evaluated by enzyme-linked immunosorbant assay.

Results: Oral mucositis rates and severity after 2 weeks were significantly lower in the OLE and benzydamine groups compared to the placebo group. The IL-1β and TNF-α levels were significantly decreased in the OLE group compared to the other groups.

Conclusion: Preliminary findings indicate that OLE is effective in reducing IL-1β and TNF-α levels after chemotherapy and exert a therapeutic effect and prevent development of severe oral mucositis.

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1. Introduction

Oral mucositis is a common, debilitating, and painful side effect of chemo- and radio-therapies of head and neck malignancies (Elad et al., 2011). By virtue of their rapid mitotic rate,

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mucosal cells in the lining of gastrointestinal tract are natural targets of cancer cytotoxic regimens (Raber-Durlacher et al., 2010). At the clinical level, oral mucositis typically manifests as atrophy, swelling, erythema, and ulceration. The condition may be exacerbated by local factors, such as trauma from teeth, or microbial colonization (Raber-Durlacher et al., 2010). Oral mucositis has a significant impact on the patient's quality of life. Severe oral mucositis is one of the leading causes of unplanned treatment interruption, chemotherapeutic dose reductions, and changes in the selection of anti-neoplastic agents (Chen et al., 2011).

Recently, a biological model for chemotherapy- and radiotherapy-induced oral mucositis was proposed by Sonis et al. (2004), which revealed the complexity of the pathogenesis of this disease. The model described mucositis events in 5 overlapping phases: initiation, signaling with messenger generation, amplification, ulceration, and healing, with pro-inflammatory cytokines playing an important role. Cytokine release can lead to tissue injury, apoptosis, and loss of epithelial integrity, with consequent ulcer development. Due to the complex pathological process of oral mucositis, no intervention is available to prevent or treat the condition on its own. Many interventions can be found in the literature, including some that may be highly protective in one set of circumstances, but have little or no effect or may even be detrimental in others (Duncan and Grant, 2003). Researchers have suggested the need to combine interventions that act on different phases of mucositis (Rodriguez-Caballero et al., 2012).

Palifermin is among the recent target therapies for mucositis. This drug alters the cytokine profiles, specifically down-regulating tumor necrosis factor (TNF) (Potting et al., 2006; Logan et al., 2007). This finding has provided further support for the role of cytokines in the development of mucosal toxicity (Spielberger et al., 2004; Potting et al., 2006). Benzydamine hydrochloride, an oral rinse with analgesic, anesthetic, anti-inflammatory, and antimicrobial activities (Sonis, 2004; Silverman, 2007), has been shown to decrease the risk of oral mucositis development in several clinical settings (Kim et al., 1986; Prada and Chiesa, 1987; Epstein et al., 1989). It also appears to reduce erythema and ulceration after radiotherapy (Epstein et al., 2001) and chemotherapy (Cheng, 2004; Cheng et al., 2004).

Olive leaf extract (OLE) is a natural product that has been used as a medicament since ancient times. Throughout history, the olive plant has been an important source of nutrition and medicine. The therapeutic use of the olive plant has even been mentioned in Holy books. OLE exerts antioxidant (Visioli and Galli, 2002), anti-inflammatory (de la Puerta et al., 2000), and antimicrobial activities against bacteria (Walker, 1996), viruses (Lee-Huang et al., 2007), fungi, and mycoplasma (Aziz et al., 1998; Markin et al., 2003). Traditionally, OLE has been used to treat and prevent hypertension through its hypoglycemic, antiseptic, and diuretic properties (Coni et al., 2000; Manna et al., 2004; Andreadou et al., 2007; Singh et al., 2008). Recent studies have demonstrated the anticancer effects of OLE (Hamdi and Castellon, 2005; Abaza et al., 2007). For example, Atai et al. (2007) compared topical OLE with topical dexamethasone elixir for the treatment of recurrent aphthus ulceration, finding that both medications similarly reduced ulcer size and decreased pain. Only one study has examined the effect of OLE in reducing cancer-related complications; a doctoral dissertation study by Talabani et al. (2010) evaluated the effect of OLE in preventing and treating oral mucositis.

To our knowledge, no study in the literature has evaluated the effect of OLE on pro-inflammatory cytokine expression in cancer patients receiving chemotherapy. Accordingly, the purpose of this study was to investigate the ability of OLE to prevent or delay the appearance of severe oral mucositis in cancer patients receiving chemotherapy. Its effect was compared with that of benzydamine hydrochloride as a positive control and placebo as a negative control. Cytological assays were used to examine the effects of the drugs on the profiles of two pro-inflammatory cytokines: interleukin-1 beta (IL-1β) and TNF alpha (TNF-α).

2. Patients, materials, and methods

2.1. Setting and patients

The study was carried out at the Hiwa Oncology Hospital in Sulaimani City (Kurdistan region/Iraq) between December 2011 and June 2012. Twenty-five consecutive cancer patients (children and adults) who were under intensive cancer treatment participated in this study. All procedures were conducted in accordance with the guidelines approved by the local ethics committee of the University of Sulaimani. Fig. 1 shows a schematic for the design of the study.

The inclusion criteria of this study were as follows: (1) patients receiving intensive cancer treatment (high dose of a single cytotoxic drug or combinations of multiple cytotoxic drugs); (2) absence of prophylactic local treatment for mucositis; and (3) informed consent provided by the patient or their parents/guardians. A patient was excluded from participation in the study if any of the following exclusion criteria applied: (1) patients under non-intensive chemotherapeutic treatment; (2) patients taking prophylactic local medication for oral mucositis; and (3) patients who requested to leave or be excluded from the study.

2.2. Study design

A prospective, randomized, double-blind, placebo-controlled, cross-over study design was selected. There were a few reasons for the choice of study design. First, it was extremely difficult to control for all therapy- and patient-specific variables in a single-center study. Second, from a practical perspective, it was difficult to obtain sufficient numbers of participants in the study time period who met all of the inclusion criteria.

2.3. Oral treatment regimen

Mouth rinse solutions

- OLE (333 mg/ml *Olea europaea L.*, St. Francis Herb Farm Inc. Combermere, Canada)
- Benzydamine hydrochloride (0.15 g/100 ml, EPICO, Egypt; under License of F.ANGELINI ITALY®).
- Normal saline, as placebo.

Eligible patients were randomized to receive benzydamine hydrochloride, OLE, or placebo in the form of a mouth rinse. This oral treatment was changed in the next chemotherapy cycle for each patient (cross-over design). The studied drugs were self-administered 3–4 times daily for 14 days, starting on the