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Review article

Leukemia

Methotrexate-associated oral mucositis in children with acute lymphoblastic leukemia

Ewa Pustelnik[1], Katarzyna Pikora[1], Katarzyna Pawelec[2]

[1]*Infant Jesus Clinical Hospital of the University Clinical Center, Medical University of Warsaw, Warsaw, Poland*
[2]*Department of Oncology, Pediatric Hematology, Clinical Transplantology and Pediatric, University Clinical Center, Medical University of Warsaw, Warsaw, Poland*

Methotrexate is an antifolate widely used in oncology and rheumatology that plays an important role in the treatment of acute lymphoblastic leukemia in children. One of its most common side effects is oral mucositis, which is a general term for ulceration and inflammation of the mucous membrane of the mouth. It can severely affect a patient's quality of life, causes poor nutrition, and may lead to discontinuation of the next course of chemotherapy. Oral mucositis typically develops a few days after chemotherapy infusion. Due to this risk, it appears reasonable to use preventive agents against oral mucositis before the inclusion of methotrexate in therapy. To date, clinical trials have examined the effectiveness of medications such as glutamine, palifermin, chlorhexidine, amifostine, cyclooxygenase-1 inhibitor, leucovorin or other methods including laser therapy and oral cryotherapy. There are also several methods used to control already established inflammation and reduce pain more effectively: laser therapy, platelet-rich plasma and platelet gel, taxifolin, film-forming and coating agents. A crucial role is played by supportive interventions involving analgesic treatment, including topical morphine and benzydamine and a modern approach to pain management – for example, the use of virtual reality.

Key words: leukemia, methotrexate, chemotherapy, oral mucositis

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant tumor in the pediatric population while it accounts for only 2% in adults [1]. Of all childhood cancers, leukemia accounts for about 26%, and ALL is the most common (about 85% of all leukemias) [2]. Intensive chemotherapy still regimens the first line of treatment of acute leukemia. However, it is not without adverse effects. The most frequent are pancytopenia, infectious disease and organ toxicity. Table I presents the side effects of frequently-used chemotherapy.

Methotrexate (MTX), an antifolate agent, is one of the most widely used and frequently studied drugs in various malignancies including leukemia and plays a crucial role in treating ALL in children. According to protocol AIEOP-BFM-2017, children in low-risk and intermediate-risk groups receive four 24 h infusions of high-dose methotrexate (HD-MTX) during Protocole M. Children in the high-risk group receive HD-MTX during the first and second HR block. All of the children receive methotrexate at a dose 20 mg/m² once a week during maintenance therapy [11].

Pathogenesis of methotrexate toxicity

Methotrexate is a folate antagonist – it inhibits dihydrofolate reductase (DHFR). This enzyme reduces folic acid to

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Table I. Common side effects of widely used chemotherapeutic drugs

Medication	Adverse effect
vinca alkaloids (e.g. vincristine) [3]	neurotoxicity (peripheral neuropathy), constipation
cyclophosphamide [4, 5]	hemorrhagic cystitis, early-onset pneumonitis, pulmonary pneumonitis
methotrexate [6, 7]	hepatic toxicity, gastrointestinal toxicity, skin and mucosa toxicity, nephrotoxicity
cytarabine [8]	ocular toxicity (corneal pain, keratoconjunctivitis, blurred vision), maculopapular rash, bone pain
PEG-asparaginase [9]	thrombosis, pancreatitis, hyperglycemia, and hepatotoxicity
anthracyclines (e.g. doxorubicin, daunorubicin) [10]	cardiomyopathy

tetrahydrofolic acid. Tetrahydrofolate has to be built up by a DHFR-catalyzed reaction. Inhibition of DHFR by methotrexate results in a deficiency of thymidylate and purines and then a decrease in nucleic acid synthesis, which leads to inhibited cells division. Methotrexate acts mainly in the "S" phase in a cell cycle, and is therefore appropriate for leukemias and lymphomas. Cytotoxic MTX occurs mainly in rapidly multiplying cells such as epithelial. These cells are susceptible to the effects of cytotoxic therapy because they undergo rapid turnover, usually every 7 to 14 days [13]. In addition, this effect can be exacerbated by bacterial or fungal infections, especially during neutropenia, which is relatively common in children with ALL.

For MTX, transport is essential to generate a sufficient quantity of intracellular drug to maximally inhibit DHFR and to provide a substrate for the synthesis of MTX polyglutamyl derivatives required for cellular drug retention as well as sustaining antitumor effects [14]. MTX enters cells through an active transporter called reduced folate carrier (RFC), a gene located on chromosome 21q22 [15]. In Down syndrome (DS), each somatic cell has an extra copy of this chromosome, resulting in an accumulation of MTX in the form of MTX polyglutamate [16]. This explains the severe toxicity of MTX in patients with DS, especially in the gastro-intestinal tract. After receiving a high-dose of 5 g/m² of MTX (HD-MTX), patients with DS showed significantly higher rates of severe leukopenia, thrombocytopenia, infections and oral mucositis compared to patients without DS, who received the same dose [17]. Knowing how the metabolism of MTX differs in children with DS, HD-MTX is administered differently in DS. According to the AIEOP-BFM-2017 protocol, children with DS receive a reduced dose of 0.5 g/m² of MTX, and then, if there is no severe toxicity, the dose is increased to 2 g/m² and finally 5 g/m² [10]. It is important to emphasize that children with DS who receive lower doses of MTX do not have a higher risk of relapse than children without DS who receive high-dose MTX. Moreover, among children with DS, there is no significant difference in the risk of relapse between children who received a first dose of MTX 0.5 g/m² and children who received MTX at a dose of 5 g/m² [18].

Methods of prevention

As mentioned, the use of methotrexate in treating ALL can cause a number of side effects, including oral mucositis with varying degrees of severity. This is a frequent complication, often contributing to a significant decrease in the patient's quality of life due to pain and difficulties with oral intake of solid foods and liquids [19]. Considering the risk of its occurrence, it is already advisable to use preventive agents against stomatitis before including methotrexate in therapy. It is not possible to achieve one-hundred percent efficacy in preventing oral mucositis (OM), but there is a chance of decreasing its occurrence and alleviating its course in ALL patients.

Glutamine

Glutamine is one of a group of conditionally essential amino acids, especially under conditions of catabolic stress, when glutamine consumption by the kidney, gastrointestinal tract and immune system compartment increases rapidly. These observations reflect the dependence of growing cancer cells on glutamine, with some cancer cells dying promptly while being deprived of glutamine [20]. On the other hand, glutamine can regulate the inflammatory response and immune balance, reduce intestinal damage, maintain the intestinal mucosal barrier and reduce the translocation of the microbiota of the intestine [21]. From an analysis of the available literature, it was concluded that oral glutamine supplementation may be reasonable for the prevention of OM.

Gaurav et al. summarized the metabolism and therapeutic applicability of glutamine on animal models. They reported that this substance reduces the immunosuppressive effect of MTX, reducing the incidence of side effects including the inflammation of mucous membranes, especially the intestinal epithelium, as well as the oral cavity [22]. Another study compared the effectiveness of parenteral glutamine in patients with ALL receiving HD-MTX in consolidation therapy. In the study group, glutamine administration was initiated within 48 h of the start of chemotherapy and continued for 3 days. It was found that the incidence of OM was considerably lower in this group than in the control group, in which patients did not

receive glutamine. There was no severe oral mucositis in any patient in the study group. Moreover, no severe adverse reactions related to glutamine administration were reported [23]. Widjaja et al. conducted a similar study, but in the study group, they included oral glutamine 24 h before HD-MTX administration and continued its administration for 14 days. As a result, oral mucositis occurred in 4.2% in the glutamine group and 62.5% in the group receiving the placebo. Additionally, the duration of hospitalization of children taking glutamine was significantly shorter. That leads to the conclusion that glutamine may be an effective and safe adjunct in the future for preventing mucositis during MTX chemotherapy [24].

Palifermin

Palifermin is a recombinant human keratinocyte growth factor (KGF) with cytoprotective effects. It has been shown to stimulate epithelial cell proliferation in many tissues of the organism. It binds to specific receptors on the surface of cells that line the mouth, stomach and intestines. This potentially may help protect healthy tissues from certain side effects caused by certain types of cancer treatment [25].

One research study from 2016 investigated the efficacy of palifermin in preventing oral mucositis in children with ALL by intravenous administration 3 days before and 3 days after chemotherapy. Children in the study group had significantly less frequent and less severe mucositis (none had WHO grade III or IV mucositis) [26]. The clinical study by Schmidt et al. examined pediatric patients with ALL who developed severe oral mucositis (WHO grade III–IV) at the first stage of therapy. They were then administered palifermin with subsequent similar cycles of chemotherapy. The incidence of mucositis decreased significantly, and its duration shortened. This confirmed the hypothesis that palifermin could reduce the incidence, severity and duration of OM in HD-MTX-based chemotherapy and have a beneficial effect on patients' quality of life [27].

Laser therapy

Low-level laser therapy (LLLT), also known as photobiomodulation therapy (PBMT), is a non-invasive method of preventing and treating mucositis by applying a high-density monochromatic narrow-band light source of varying wavelengths (630–830 nm) to the mucosa. The proven clinical efficacy of PBMT in preventing mucositis has led to its increasing use in pediatric oncology [28]. Several studies have been published demonstrating the effectiveness of prophylactic laser therapy in children with ALL undergoing MTX treatment. One of them retrospectively examined the association of OM with PBMT in several pediatric oncology disease entities. MTX was the second most frequent cause of OM. PBMT significantly reduced the severity and incidence of OM in patients with ALL [29]. A study by de Castro et al. compared the course of chemotherapy treatment in patients using prophylactic oral laser therapy and laser therapy included only after the onset of OM symptoms. Summarizing the results, laser therapy has been proven effective in the treatment and prevention of OM, but prophylactic treatment resulted in better clinical outcomes at the end of treatment [30].

In contrast, another study compared the clinical outcomes of pediatric oncology patients receiving or not receiving prophylactic lasotherapy. Tests on a group of 60 patients indicated no evidence of benefit from such treatment in children with chemotherapy-treated malignancy, especially when optimal dental and oral care was ensured [31].

Chlorhexidine

Chlorhexidine is an antiseptic solution used topically for various purposes, such as preoperative skin preparation, hand washing, vaginal antisepsis or treatment of gingivitis. It has broad spectrum activity against gram-positive and gram-negative bacteria, facultative anaerobes and aerobes, yeasts and certain lipid-bound viruses [32]. In view of this microbial-destroying effect, an attempt was made to implement chlorhexidine in the prevention of oral mucositis in oncology patients.

In the first trial, 0.12% chlorhexidine gluconate was administered to a study group of children with ALL for 10 days after each MTX infusion. Among these patients, a quarter developed grade I OM. In the control group, signs of inflammation appeared in 80% and were more severe [33]. A similar study was conducted among patients at a Brazilian Medical Center, with comparable results – a significant reduction in the incidence of OM was noted in children who received 0.12% chlorhexidine mouthwash during intensive chemotherapy [34]. Soares et al. conducted a study evaluating clinical and microbiological changes in the oral mucosa of children with ALL during chemotherapy and after prophylactic use of chlorhexidine. Only five children developed features of OM, and microbiological tests resulted in a reduced number of pathogenic microorganisms, including coagulase-negative staphylococci, *Candida albicans*, E. coli and Stenotrophomonas maltophilia. No control group was formed in the study [35]. The results presented above suggest that systematic prophylactic treatment with the chlorhexidine compound and careful attention to oral hygiene reduce the incidence of oral complications in children with ALL undergoing antineoplastic chemotherapy.

Other

A few single reports on other medical agents were also found, which may in future provide a basis for expanding research on their effectiveness in preventing OM.

Leucovorin is a derivative of folic acid used in the treatment of methotrexate toxicity and chemotherapy regimens [36]. The administration of leucovorin during MTX treatment increases cellular folate levels, so it has been hypothesized that this may further contribute to the reduced incidence of OM after subsequent courses of MTX [37].

In pathogenesis, methotrexate-induced oral mucositis is thought to develop through epithelial damage by reactive

oxygen species, disruption of cell growth and apoptosis or necrosis. This exposes the mucous membranes to oral infections caused by bacteria and fungi. The administration of MTX leads to an increase in oxidative stress and, consequently, cytotoxicity [38]. A study by Maiguma et al. examined the prophylactic use of a free radical scavenger (amifostine) and a cyclooxygenase-1 inhibitor as a disruptor of hydroxyl radical production. From an electron spin resonance study, it was found that methotrexate-induced cell damage was restored by amifostine and cyclooxygenase-1 inhibitor, and it was suggested that they may be useful protective agents against the chemotherapeutic toxicity of this drug [39].

The last preventive method suggested will be cryotherapy, which involves patients holding ice-chips in their mouths continuously during chemotherapy. No scientific studies have been found proving the efficacy of this method for MTX treatment, but several research papers have demonstrated its effectiveness against other chemotherapeutics, such as 5-FU or mephalan, and during conditioning before HSCT. It is assumed that ice causes local vasoconstriction, which reduces drug delivery to the oral mucosa tissues and therefore reduces the risk of OM. In the cited studies, patients in the study group developed severe OM less often, required less intensive and shorter analgesic treatment, and avoided the need for TPN. This leads to the hypothesis that it is advisable to conduct further randomized studies examining the beneficial effects of cryotherapy on OM caused also by other medications, including MTX [40–43].

Clinical picture

MTX-associated oral mucositis typically develops a few days after chemotherapy. Symptoms are varied, ranging from mild soreness in the mouth to severe symptoms requiring total parenteral nutrition. The most common symptom is pain requiring analgesics. Other symptoms include: burning sensation in the mouth, difficulty swallowing leading to cessation of water and food intake. Changes in the oral mucosa develop from redness to ulcers. Due to pancytopenia after chemotherapy, bleeding from the ulcers may occur [44]. According to the WHO toxicity grading scale there are four grades of presence of oral mucositis:

I. oral soreness, erythema,
II. oral erythema, ulcers,
III. oral ulcers, only liquids intake (due to the mucositis),
IV. oral ulcers, oral alimentation impossible (due to the mucositis) [45].

In the next figures (fig. 1–8) four grades of MTX-oral mucositis in children with ALL are presented. The source of all the photographs is the authors

Treatment of oral mucositis

A completely effective method of treating OM after chemotherapy has not been developed to date. There are several medications used to manage inflammation and reduce pain more quickly, as further described below. However, none provide certain efficacy and they are not widely published in treatment protocols. Therapeutic management is therefore based on agents that regenerate the oral mucosa and reduce inflammation. In addition, supportive treatment in the form of analgesics, antibacterials, antifungals, dietary modification, including total parenteral nutrition, and changes in oral hygiene are practiced.

Laser therapy

Different biological effects have been described to explain the mechanism of laser therapeutic efficacy: increased collagen production, the activation of energy production in the mitochondria, the detoxification of free radicals, the proliferation of fibroblast cells and stimulation of angiogenesis [28]. The literature examining the efficacy of LLLT in treating OM in a population of children with ALL was analyzed by the authors.

The first cited randomized clinical trial was conducted by Reyad et al. on a group of 14 patients. The study group was undergoing treatment with PBMT in addition to standard symptomatic therapy. There was a significant reduction in the severity

Figure 1. Oral mucositis grade I: erythema can be seen on the soft palate and upper labia; the patient complained of soreness on swallowing

Figure 2. Oral mucositis grade II: erythema and ulcers can be seen in the labias

Figure 3. Oral mucositis grade II: erythema and ulcers can be seen in the buccal mucosa

Figure 4. Oral mucositis grade III: ulcers with extensive erythema can be seen

Figure 5. Oral mucositis grade III: ulcers with extensive erythema can be seen. Only liquid food intake

Figure 6. Oral mucositis grade IV: generalized ulcers, erythema. Bleeding from the labias. Nourishing was no longer possible for this patient. Total parenteral nutrition was started

Figure 7. Oral mucositis grade IV: generalized ulcers, erythema, leukemia

Figure 8. Oral mucositis grade IV: generalized ulcers, erythema, leukemia. yellow coating after antifungals

of pain on the 10th day of treatment and a reduction in the degree of OM on the 14th day of treatment compared to the control group [46]. Another trial compared the use of LLLT or placebo in cancer patients receiving chemotherapy or hematopoietic stem cell transplantation; 86% of the participants were leukemia patients. In the laser-treated group, the average duration of OM to resolution of clinical symptoms was significantly shorter [47]. Other clinical studies by Cauwels et al., Karaman et al. and Fiwek et al. conducted similar clinical proceedings to those presented earlier. All obtained results confirmed that the use of PBMT reduces pain and discomfort in patients and has a positive effect on the severity and duration of OM [48–50].

Platelet-rich plasma and platelet gel

Platelet-rich plasma (PRP) contains a platelet concentration five times higher than the baseline, cytokines, growth factors, adhesion molecules, a certain amount of red blood cells (RBCs) and white blood cells (WBCs) depending on the preparation method. It is obtained from fresh peripheral blood with a platelet concentration above the baseline value [51]. Platelet gel (PG) is derived from PRP and consists of platelet concentrate (PC) deposited in a semisolid network of polymerized fibrin. The biological reasoning behind the use of PRP and PG in regenerative medicine is related to the degranulation of platelets, allowing the release of growth factors, reducing the inflammatory response and promoting cell proliferation and differentiation in the targeted tissue. Use of PRP has broadened considerably to encompass many fields of medicine, including dermatology, orthopedics, surgery, sports medicine, aesthetic medicine and dentistry [52]. Some reports have also been published about the efficacy of these agents in reducing neuropathic and neurological pain associated with injuries. The use of platelet concentrates accelerates the healing of surgical wounds, skin ulcers, lesions typical of diabetic foot and chronic mucositis, as well as muscle and tendon repair [53].

Within the last few years, there has also been an attempt to use this agent in the field of oncology, including pediatrics. Piccin et al. examined the effectiveness of PG in treatment of severe oral and esophageal mucositis in an adult patient undergoing auto-HSCT for non-Hodgkin lymphoma. The patient self-administered the preparation in her oral cavity. A significant improvement in mucositis and pain was noted after only 3 days of consecutive use. On day 8, the inflammation was found to have regressed. No side effects of the preparation were observed [54]. Another study described a five-year-old girl with rhabdomyosarcoma undergoing intensive chemotherapy who developed stage IV OM with severe pain and fever during the second course of treatment. She was treated with antimicrobial drugs, analgesics, chlorhexidine and oral rinses, but no improvement was observed after three days of therapy. The decision was made to start a thrice-daily oral application of platelet gel. After just 12 h, significant improvement in mucosal condition was observed, and two days later the patient did not require analgesic treatment, was able to receive oral nutrition, continue chemotherapy treatment, and the oral ulcers were progressively improving [55].

Picardi et al. conducted a study on an Italian group of patients affected by hematologic malignancies and who after allo-HSCT developed cGvHD with oral involvement in the form of painful ulcers and impaired oral nutrition. Limited oral ulceration cGvHD was treated with PG alone, while the most extensive cGvHD received PG in combination with steroids. The results indicated that all patients treated with PG achieved rapid improvement in oral pain and food intake after just 2 applications of the gel. The absence of ulcer recurrence at the site of previous platelet gel application proves that its growth factor-rich content makes it a viable tool for maintaining long-term tissue repair [56]. The 2021 clinical trial studied the effectiveness of platelet gel in children with stage II and III OM during chemotherapy. In the study group, PG was applied to mucosal lesions four times a day in addition to standard treatment including analgesics, antimicrobials, and oral rinses. In almost all patients, the application of PG provided relief, reduced pain and decreased any burning sensation after the first day of application. In addition, there was a significant improvement in the appearance of the mucous membranes and regression of the inflammatory lesions within 4–5 days [57].

Other

There are several other individual, insufficiently researched ideas and treatments for OM. Additional scientific studies reporting innovative treatment attempts are presented and summarized hereafter.

Taxifolin is a bioactive flavonoid found commonly in grapes or olive oil, among others, with well-established pharmacological effects, including having anti-inflammatory, antioxidant properties, and also antimicrobial and anticancer potential. It reduces oxidative stress, modulates signaling pathways to prevent apoptosis and decreases the expression of pro-inflammatory cytokines [58, 59]. Bayramoglu et al. conducted a study on MTX-treated rats, administering taxifolin by gavage. The oral mucosa was subsequently analyzed macroscopically, histopathologically and biochemically. It was found that taxifolin antagonized the MTX-induced increase in oxidative and pro-inflammatory factors and decrease in antioxidant properties in the internal tissues of the cheek and tongue. Taxifolin also significantly reduced histopathological damage induced by MTX administration. The results suggest that taxifolin may be useful in the treatment of MTX-induced oral mucositis [60].

Film-forming or coating agents might also be useful for the treatment of established mucositis. These include sucralfate and hydroxypropyl cellulose, whose efficacy in reducing OM has been clinically studied. An initial randomized clinical trial reported good outcomes in reducing the severity of OM in a patient population treated with chemotherapy (5-fluorouracil) after treatment with sucralfate. However, a subsequent double-blind phase III study did not support the hypothesis from the initial study, as there were no differences in the severity or duration of inflammation between the study and placebo group [61]. Hydroxypropyl cellulose is a bioadhesive substance that can function as a protective barrier over mucosal ulceration enabling pain relief and improved healing. The study group included chemotherapy-treated patients with symptoms of OM. After application of the gel with hydroxypropyl cellulose and benzocaine hydrochloride, oral pain and discomfort were assessed using a visual analog scale (VAS) and visual assessments of the amount of drug that remained on the mucosal lesions. Benzocaine hydrochloride, combined with a protective, mucoadhesive film coating, alleviated discomfort even with

exposure to an irritating beverage. This indicates that the administered treatment may enable patients with OM to drink and eat with significantly reduced or no pain. However, the results are difficult to interpret due to the use of a gel combining two active substances in the study group [13, 62].

Pain management

Pain may be the only symptom of OM, although it is usually the first of many. The crucial issue remains to control it effectively, as severe pain impairs food and drink intake, which may result in malnutrition and mineral deficiencies. In addition to the classic analgesic ladder approach in children, additional less-known pain management methods are presented, including topical analgesics and the use of virtual reality.

Topical morphine

The use of non-opioid topical analgesics can reduce the dose of systemic opioids. Compared to their administration, topical morphine has been shown to have even more beneficial effects. These include simplicity of use, low cost and minimal systemic side effects. The benefits are not only related to pain relief. There is also some evidence that opioid receptors are expressed on oral epithelial cells and morphine may accelerate cell migration, which in turn can enhance the wound healing process. Topical morphine is applied as a solution to swish and spit. There have been studies on the selection of the most effective percentage solution. Sarvizadeh et al. reported that 2% morphine was effective in reducing the severity of OM. However, its use with a pediatric population suffering from ALL is unknown. MASCC/ISOO suggest 0.2% topical morphine mouthwash for the treatment of OM-associated pain in head and neck cancer patients treated with RTX/CTX [63, 64].

Benzydamine

Benzydamine is a local anti-inflammatory drug that also has analgesic properties. It is an inhibitor of leukocyte-endothelial interactions, neutrophil degranulation, vasodilation and vascular permeability. It also reduces the synthesis of TNF-α, IL-1β and prostaglandins [65]. Although it is widely used in radiotherapy-induced OM, there is still no strong evidence for its use in hematologic malignancies. However, given that it is feasible, inexpensive and frequently administered in pediatrics, more studies are needed in children with ALL [66].

Virtual reality

Virtual reality (VR) is a feasible, non-pharmacological method of distraction and adjustment to conventional pain management. VR is a digital simulation. It can be either immersive (IVR) or non-immersive, depending on the patient's point of view and the experience created during use. Non-immersive VR allows content to be viewed through traditional graphical displays, such as a TV or smartphone, while IVR includes head-mounted glasses and motion tracking systems. This allows full immersion to be attained. VR distraction has the potential to manage pain and anxiety in children with hematological cancers [67].

Virtual reality can be used for more than just the management of chronicling pain associated with malignant disease. It has been tested in patients undergoing painful procedures, such as burn wound care, with the following results: reduced pain scores and decreased use of opioids [68]. The aforementioned results indicate that this use of virtual reality may prove helpful during the treatment of children with oral mucositis. This distraction and diversion may be particularly important during procedures that increase a child's pain sensation associated with oral interventions, which include physical examination, mouth rinsing or application of topical medications.

Conclusions

Methotrexate, an antifolate agent, is one of the most widely used drugs in various malignancies and plays a crucial role in treating ALL in children. Patients with Down syndrome have an extra copy of the gene responsible for encoding the transporter for methotrexate, resulting in a significant increase in the toxicity of the drug in this group. One of the most frequent side effects following its administration is inflammation of the mucosa, including the oral cavity. Clinical trials have evaluated the effectiveness of medications such as glutamine, palifermin, chlorhexidine, amifostine, cyclooxygenase-1 inhibitors, leucovorin, or other methods including laser therapy and oral cryotherapy in preventing OM. Typically, oral mucositis develops a few days after chemotherapy. Symptoms are varied, ranging from mild soreness in the mouth to erythema, ulcers and severe pain. There are several methods used to control established inflammation and reduce pain more effectively: laser therapy, platelet-rich plasma and platelet gel, taxifolin, film-forming and coating agents. Crucial support is offered by interventions involving analgesic treatment, including topical morphine and benzydamine and a more recent approach based on virtual reality, for example.

Article information and declarations

Author contributions

Katarzyna Pawelec – conceptualization, review and editing. Ewa Pustelnik, Katarzyna Pikora – methodology, formal analysis, investigation, original draft preparation.

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Ewa Pustelnik
Medical University of Warsaw
Infant Jesus Clinical Hospital of the University Clinical Center
ul. Lindleya 4
02-005 Warszawa, Poland
e-mail: ewa.pustelnik1994@gmail.com

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References

1. Wojciechowska U, Barańska K, Miklewska M, et al. Cancer incidence and mortality in Poland in 2020. Nowotwory. Journal of Oncology. 2023; 73(3): 129–145, doi: 10.5603/njo.2023.0026.
2. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014; 64(2): 83–103, doi: 10.3322/caac.21219, indexed in Pubmed: 24488779.
3. Brigo F, Balter R, Marradi P, et al. Vincristine-related neuropathy versus acute inflammatory demyelinating polyradiculoneuropathy in children with acute lymphoblastic leukemia. J Child Neurol. 2012; 27(7): 867–874, doi: 10.1177/0883073811428379, indexed in Pubmed: 22241706.
4. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum. 2010; 62(1): 9–21, doi: 10.1002/art.25061, indexed in Pubmed: 20039416.
5. Malik SW, Myers JL, DeRemee RA, et al. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. Am J Respir Crit Care Med. 1996; 154(6 Pt 1): 1851–1856, doi: 10.1164/ajrccm.154.6.8970380, indexed in Pubmed: 8970380.
6. Campbell JM, Bateman E, Stephenson MD, et al. Methotrexate-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. Cancer Chemother Pharmacol. 2016; 78(1): 27–39, doi: 10.1007/s00280-016-3043-5, indexed in Pubmed: 27142726.
7. Wiczer T, Dotson E, Tuten A, et al. Evaluation of incidence and risk factors for high-dose methotrexate-induced nephrotoxicity. J Oncol Pharm Pract. 2016; 22(3): 430–436, doi: 10.1177/1078155215594417, indexed in Pubmed: 26152702.
8. Di Francia R, Crisci S, De Monaco A, et al. Response and Toxicity to Cytarabine Therapy in Leukemia and Lymphoma: From Dose Puzzle to Pharmacogenomic Biomarkers. Cancers (Basel). 2021; 13(5), doi: 10.3390/cancers13050966, indexed in Pubmed: 33669053.
9. Earl M. Incidence and management of asparaginase-associated adverse events in patients with acute lymphoblastic leukemia. Clin Adv Hematol Oncol. 2009; 7(9): 600–606, indexed in Pubmed: 20020672.
10. Mancilla TR, Iskra B, Aune GJ. Doxorubicin-Induced Cardiomyopathy in Children. Compr Physiol. 2019; 9(3): 905–931, doi: 10.1002/cphy.c180017, indexed in Pubmed: 31187890.
11. AIEOP-BFM ALL 2017 International collaborative treatment protocol for children and adolescents with acute lymphoblastic leukemia. A randomized phase III study conducted by the AIEOP-BFM study group. Protocol version 1.3 (date 01.02.2018).
12. Naidu MU, Ramana GV, Rani PU, et al. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. Neoplasia. 2004; 6(5): 423–431, doi: 10.1593/neo.04169, indexed in Pubmed: 15548350.
13. Adam de Beaumais T, Jacqz-Aigrain E. Pharmacogenetics: Applications to Pediatric Patients. Adv Pharmacol. 2018; 83: 191–215, doi: 10.1016/bs.apha.2018.04.006, indexed in Pubmed: 29801575.
14. Matherly LH, Wilson MR, Hou Z. The major facilitative folate transporters solute carrier 19A1 and solute carrier 46A1: biology and role in antifolate chemotherapy of cancer. Drug Metab Dispos. 2014; 42(4): 632–649, doi: 10.1124/dmd.113.055723, indexed in Pubmed: 24396145.
15. Taub JW, Ge Y. Down syndrome, drug metabolism and chromosome 21. Pediatr Blood Cancer. 2005; 44(1): 33–39, doi: 10.1002/pbc.20092, indexed in Pubmed: 15390307.
16. Kroll M, Kaupat-Bleckmann K, Mörickel A, et al. Methotrexate-associated toxicity in children with Down syndrome and acute lymphoblastic leukemia during consolidation therapy with high dose methotrexate according to ALL-BFM treatment regimen. Haematologica. 2020; 105(4): 1013–1020, doi: 10.3324/haematol.2019.224774, indexed in Pubmed: 31371414.
17. Alaama J, Ahmad M, Ahmad S, et al. Altered Metabolism in Down Syndrome. Health Problems in Down Syndrome. 2015, doi: 10.5772/60638.
18. Sun Q, Xie Y, Zhao WH, et al. [Adverse effects of high-dose methotrexate therapy]. Zhongguo Dang Dai Er Ke Za Zhi. 2017; 19(7): 781–785, doi: 10.7499/j.issn.1008-8830.2017.07.010, indexed in Pubmed: 28697831.
19. Altman BJ, Stine ZE, Dang CV, et al. From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer. 2016; 16(10): 619–634, doi: 10.1038/nrc.2016.71, indexed in Pubmed: 27492215.
20. Tang G, Pi F, Qiu YH, et al. Postoperative parenteral glutamine supplementation improves the short-term outcomes in patients undergoing colorectal cancer surgery: A propensity score matching study. Front Nutr. 2023; 10: 1040893, doi: 10.3389/fnut.2023.1040893, indexed in Pubmed: 37006941.
21. Gaurav K, Goel RK, Shukla M, et al. Glutamine: A novel approach to chemotherapy-induced toxicity. Indian J Med Paediatr Oncol. 2012; 33(1): 13–20, doi: 10.4103/0971-5851.96962, indexed in Pubmed: 22754203.
22. Chang YH, Yu MS, Wu KH, et al. Effectiveness of Parenteral Glutamine on Methotrexate-induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia. Nutr Cancer. 2017; 69(5): 746–751, doi: 10.1080/01635581.2017.1324995, indexed in Pubmed: 28569624.
23. Widjaja NA, Pratama A, Prihaningtyas R, et al. Efficacy Oral Glutamine to Prevent Oral Mucositis and Reduce Hospital Costs During Chemotherapy in Children with Acute Lymphoblastic Leukemia. Asian Pac J Cancer Prev. 2020; 21(7): 2117–2121, doi: 10.31557/APJCP.2020.21.7.2117, indexed in Pubmed: 32711440.
24. Coutsouvelis J, Corallo C, Spencer A, et al. A meta-analysis of palifermin efficacy for the management of oral mucositis in patients with solid tumours and haematological malignancy. Crit Rev Oncol Hematol. 2022; 172: 103606, doi: 10.1016/j.critrevonc.2022.103606, indexed in Pubmed: 35101586.
25. Gholizadeh N, Mehdipoor M, Sajadi H, et al. Palifermin and Chlorhexidine Mouthwashes in Prevention of Chemotherapy-Induced Mucositis in Children with Acute Lymphocytic Leukemia: a Randomized Controlled Trial. J Dent (Shiraz). 2016; 17(4): 343–347, indexed in Pubmed: 27942550.
26. Schmidt E, Thoennissen NH, Rudat A, et al. Use of palifermin for the prevention of high-dose methotrexate-induced oral mucositis. Ann Oncol. 2008; 19(9): 1644–1649, doi: 10.1093/annonc/mdn179, indexed in Pubmed: 18453519.
27. Legouté F, Bensadoun RJ, Seegers V, et al. Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: results of a randomised, triple blind, multicentre phase III trial. Radiat Oncol. 2019; 14(1): 83, doi: 10.1186/s13014-019-1292-2, indexed in Pubmed: 31118057.
28. Nunes LF, de Arruda JA, Souza AF, et al. Prophylactic photobiomodulation therapy using 660 nm diode laser for oral mucositis in paediatric patients under chemotherapy: 5-year experience from a Brazilian referral service. Lasers Med Sci. 2020; 35(8): 1857–1866, doi: 10.1007/s10103-020-03060-9, indexed in Pubmed: 32535807.
29. de Castro JF, Abreu EG, Correia AV, et al. Low-level laser in prevention and treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia. Photomed Laser Surg. 2013; 31(12): 613–618, doi: 10.1089/pho.2012.3327, indexed in Pubmed: 24261310.
30. Cruz LB, Ribeiro AS, Rech A, et al. Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. Pediatr Blood Cancer. 2007; 48(4): 435–440, doi: 10.1002/pbc.20943, indexed in Pubmed: 16862549.
31. Milstone AM, Passaretti CL, Perl TM. Chlorhexidine: expanding the armamentarium for infection control and prevention. Clin Infect Dis. 2008; 46(2): 274–281, doi: 10.1086/524736, indexed in Pubmed: 18171263.
32. Pereira Pinto L, de Souza LB, Gordón-Núñez MA, et al. Prevention of oral lesions in children with acute lymphoblastic leukemia. Int J Pediatr Otorhinolaryngol. 2006; 70(11): 1847–1851, doi: 10.1016/j.ijporl.2006.04.016, indexed in Pubmed: 16914211.
33. Costa EM, Fernandes MZ, Quinder LB, et al. Evaluation of an oral preventive protocol in children with acute lymphoblastic leukemia. Pesqui Odontol Bras. 2003; 17(2): 147–150, doi: 10.1590/s1517-74912003000200009, indexed in Pubmed: 14569357.
34. Soares AF, Aquino AR, Carvalho CH, et al. Frequency of oral mucositis and microbiological analysis in children with acute lymphoblastic leukemia treated with 0.12% chlorhexidine gluconate. Braz Dent J. 2011; 22(4): 312–316, doi: 10.1590/s0103-64402011000400009, indexed in Pubmed: 21861031.
35. Rider B. Leucovorin. xPharm: The Comprehensive Pharmacology Reference. 2007: 1–4, doi: 10.1016/b978-008055232-3.62968-x.
36. den Hoed MAH, Lopez-Lopez E, te Winkel ML, et al. Genetic and metabolic determinants of methotrexate-induced mucositis in pediatric acute lymphoblastic leukemia. Pharmacogenomics J. 2015; 15(3): 248–254, doi: 10.1038/tpj.2014.63, indexed in Pubmed: 25348617.
37. Babiak R, Campello A, Carnieri E, et al. Methotrexate: pentose cycle and oxidative stress. Cell Biochemistry and Function. 1998; 16(4): 283–293, doi: 10.1002/(sici)1099-0844(1998120)16:4<283::aid-cbf801>3.0.co;2-e.
38. Maiguma T, Kaji H, Makino K, et al. Protective effects of amifostine and cyclooxygenase-1 inhibitor against normal human epidermal

keratinocyte toxicity induced by methotrexate and 5-fluorouracil. Basic Clin Pharmacol Toxicol. 2009; 105(1): 1–9, doi: 10.1111/j.1742-7843.2009.00400.x, indexed in Pubmed: 19371262.
39. Lilleby K, Garcia P, Gooley T, et al. A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2006; 37(11): 1031–1035, doi: 10.1038/sj.bmt.1705384, indexed in Pubmed: 16633359.
40. Aisa Y, Mori T, Kudo M, et al. Oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. Support Care Cancer. 2005; 13(4): 266–269, doi: 10.1007/s00520-004-0726-y, indexed in Pubmed: 15668755.
41. Cascinu S, Fedeli A, Fedeli SL, et al. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. Eur J Cancer B Oral Oncol. 1994; 30B(4): 234–236, doi: 10.1016/0964-1955(94)90003-5, indexed in Pubmed: 7950836.
42. Rocke L, Loprinzi C, Lee J, et al. A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. Cancer. 1993; 72(7): 2234–2238, doi: 10.1002/1097-0142(19931001)72:7<2234::aid-cncr2820720728>3.0.co;2-n.
43. Bruya MA, Madeira NP. Stomatitis after chemotherapy. Am J Nurs. 1975; 75(8): 1349–1352, indexed in Pubmed: 1041191.
44. World Health Organization: WHO Offset Publication. World Health Organization (1979).
45. Reyad FA, Elsayed NM, El Chazli Y. Photobiomodulation for chemotherapy-induced oral mucositis in leukemic children: A randomized controlled clinical trial. Oral Dis. 2023; 29(5): 2239–2247, doi: 10.1111/odi.14217, indexed in Pubmed: 35460304.
46. Kuhn A, Porto FA, Miraglia P, et al. Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. J Pediatr Hematol Oncol. 2009; 31(1): 33–37, doi: 10.1097/MPH.0b013e318192cb8e, indexed in Pubmed: 19125084.
47. Cauwels RG, Martens LC. Low level laser therapy in oral mucositis: a pilot study. Eur Arch Paediatr Dent. 2011; 12(2): 118–123, doi: 10.1007/BF03262791, indexed in Pubmed: 21473845.
48. Karaman K, Sarica A, Tunc SK, et al. Is Low-level Laser Therapy a Candidate to Be a Good Alternative in the Treatment of Mucositis in Childhood Leukemia? J Pediatr Hematol Oncol. 2022; 44(1): e199–e203, doi: 10.1097/MPH.0000000000002306, indexed in Pubmed: 34986132.
49. Fiwek P, Emerich K, Irga-Jaworska N, et al. Photobiomodulation Treatment in Chemotherapy-Induced Oral Mucositis in Young Haematological Patients-A Pilot Study. Medicina (Kaunas). 2022; 58(8), doi: 10.3390/medicina58081023, indexed in Pubmed: 36013491.
50. Ban Y, Yang X, Xing Y, et al. Intrauterine Infusion of Leukocyte-Poor Platelet-Rich Plasma Is an Effective Therapeutic Protocol for Patients with Recurrent Implantation Failure: A Retrospective Cohort Study. J Clin Med. 2023; 12(8), doi: 10.3390/jcm12082823, indexed in Pubmed: 37109159.
51. Sriram S, Hasan S, Alqarni A, et al. Efficacy of Platelet-Rich Plasma Therapy in Oral Lichen Planus: A Systematic Review. Medicina (Kaunas). 2023; 59(4), doi: 10.3390/medicina59040746, indexed in Pubmed: 37109704.
52. Piccin A, Di Pierro AM, Canzian L, et al. Platelet gel: a new therapeutic tool with great potential. Blood Transfus. 2017; 15(4): 333–340, doi: 10.2450/2016.0038-16, indexed in Pubmed: 27483482.
53. Piccin A, Rebulla P, Pupella S, et al. Impressive tissue regeneration of severe oral mucositis post stem cell transplantation using cord blood platelet gel. Transfusion. 2017; 57(9): 2220–2224, doi: 10.1111/trf.14205, indexed in Pubmed: 28656652.
54. Aielli F, Giusti R, Rughetti A, et al. Rapid resolution of refractory chemotherapy-induced oral mucositis with platelet gel-released supernatant in a pediatric cancer patient: a case report. J Pain Symptom Manage. 2014; 48(5): e2–e4, doi: 10.1016/j.jpainsymman.2014.06.015, indexed in Pubmed: 25131890.
55. Picardi A, Ferraro AS, Miranda M, et al. Therapeutic efficiency of platelet gel for the treatment of oral ulcers related to chronic graft versus host disease after allogeneic haematopoietic stem cell transplantation. Oral Implantol (Rome). 2017; 10(4): 398–405, doi: 10.11138/orl/2017.10.4.398, indexed in Pubmed: 29682257.
56. Albrecht K, Łaguna P, Lachert E, et al. Efficacy of Platelet Gel in Children with Stomatitis during Chemotherapy. Postepy Hig Med Dosw. 2021; 75(1): 720–723, doi: 10.2478/ahem-2021-0019.
57. Althunibat OY, Abukhalil MH, Jghef MM, et al. Hepatoprotective effect of taxifolin on cyclophosphamide-induced oxidative stress, inflammation, and apoptosis in mice: Involvement of Nrf2/HO-1 signaling. Biomol Biomed. 2023; 23(4): 649–660, doi: 10.17305/bb.2022.8743, indexed in Pubmed: 36762432.
58. Alaswad HA, Mahbub AA, Le Maitre CL, et al. Molecular Action of Polyphenols in Leukaemia and Their Therapeutic Potential. Int J Mol Sci. 2021; 22(6), doi: 10.3390/ijms22063085, indexed in Pubmed: 33802972.
59. Bayramoglu Z, Mokhtare B, Mendil AS, et al. Effect of taxifolin on methotrexate-induced oxidative and inflammatory oral mucositis in rats: biochemical and histopathological evaluation. J Appl Oral Sci. 2022; 30: e20220115, doi: 10.1590/1678-7757-2022-0115, indexed in Pubmed: 36134855.
60. Loprinzi CL, Ghosh C, Camoriano J, et al. Phase III controlled evaluation of sucralfate to alleviate stomatitis in patients receiving fluorouracil-based chemotherapy. J Clin Oncol. 1997; 15(3): 1235–1238, doi: 10.1200/JCO.1997.15.3.1235, indexed in Pubmed: 9060567.
61. LeVeque FG, Parzuchowski JB, Farinacci GC, et al. Clinical evaluation of MGI 209, an anesthetic, film-forming agent for relief from painful oral ulcers associated with chemotherapy. J Clin Oncol. 1992; 10(12): 1963–1968, doi: 10.1200/JCO.1992.10.12.1963, indexed in Pubmed: 1453210.
62. Saunders DP, Rouleau T, Cheng K, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2020; 28(5): 2473–2484, doi: 10.1007/s00520-019-05181-6, indexed in Pubmed: 32052137.
63. Sarvizadeh M, Hemati S, Meidani M, et al. Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. Adv Biomed Res. 2015; 4: 44, doi: 10.4103/2277-9175.151254, indexed in Pubmed: 25789270.
64. Nicolatou-Galitis O, Bossi P, Orlandi E, et al. The role of benzydamine in prevention and treatment of chemoradiotherapy-induced mucositis. Support Care Cancer. 2021; 29(10): 5701–5709, doi: 10.1007/s00520-021-06048-5, indexed in Pubmed: 33649918.
65. Epstein J, Silverman S, Paggiarino D, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis. Cancer. 2001; 92(4): 875–885, doi: 10.1002/1097-0142(20010815)92:4<875::aid-cncr1396>3.0.co;2-1.
66. Comparcini D, Simonetti V, Galli F, et al. Immersive and Non-Immersive Virtual Reality for Pain and Anxiety Management in Pediatric Patients with Hematological or Solid Cancer: A Systematic Review. Cancers (Basel). 2023; 15(3), doi: 10.3390/cancers15030985, indexed in Pubmed: 36765945.
67. Hoffman HG, Richards TL, Van Oostrom T, et al. The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. Anesth Analg. 2007; 105(6): 1776–83, table of contents, doi: 10.1213/01.ane.0000270205.45146.db, indexed in Pubmed: 18042882.