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Administration of Samital® in children with oral mucositis: a feasibility study

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Abstract. – OBJECTIVE: SAMITAL®, a botanical drug containing three highly standardized extracts (*Vaccinium myrtillus, Macleaya cordata and Echinacea angustifolia*), has shown promising results in treating or preventing oral mucositis (OM) in adult patients, but it has not been fully investigated in children. In this study, we assessed the feasibility of SAMITAL administration in pediatric patients receiving anticancer treatment to prevent or treat OM, focusing on identifying an appropriate dose and evaluating safety and tolerability and palatability and treatment compliance.

PATIENTS AND METHODS: We conducted an open-label, monocentric, prospective study on 18 children receiving anticancer therapy to prevent or treat OM.

RESULTS: No SAMITAL®-related side effects were observed or reported during the study; moreover, no systemic absorption of SAMITAL® metabolites was detected in the bloodstream. However, compliance to SAMITAL® was unsatisfactory and variable (from 2 to 100%), and patients reported low palatability (median taste of 4.8; range 1.0-8.0).

CONCLUSIONS: SAMITAL® administration appears to be safe in the pediatric population, as it is not absorbed in the bloodstream and does not cause any local or systemic side effects. However, the current formulation is only partially suitable for children, and future studies on SAMITAL® in children would need an adapted formulation to increase compliance.

Key Words:
Mucositis, Pediatrics, Quality of life, SAMITAL®, Supportive care.

Abbreviations

AIFA: Italian Medicines Agency; HPLC/MS: high-performance liquid chromatography-tandem mass spectrometry; LLOQ: lower limit of quantification; OM: Oral mucositis.

Introduction

Oral mucositis (OM) represents one of the most common side effects of anticancer treatments in children, resulting from chemotherapy- and radiotherapy-induced damage to oral epithelial cells[1]. The clinical manifestations of OM range from mild mucosal inflammation to deep ulcers, which cause severe oral pain, impaired food and liquids intake and increased risk of infection. These may, in turn, lead to prolonged hospital stays, a decrease in patients' quality of life, a potential delay of anticancer treatments and an increased risk of life-threatening bacteremia[2,3].

Different strategies and drugs have been tested to prevent OM or treat adults with OM[4], whereas only a few studies[5-7] have been conducted to treat or prevent OM in children. Initial studies suggested the efficacy of laser therapy in the prevention of OM in children[5,6], but a recent meta-analysis has not confirmed this[7]. Preliminary data also reported a significant decrease in the incidence of OM in children treated with palifermin, a recombinant keratinocyte growth factor approved for the treatment and prevention of OM in adults. However, its use is ultimately not recommended in the pediatric population due to a lack of long-term follow-up data and potential negative effects on cancer patients[7-9].

SAMITAL® is a promising botanical drug used for treating or preventing mucositis, which contains three highly standardized and purified botanical extracts that are classified as 'herbal drug preparation'. The three components, namely *Vaccinium myrtillus*, *Macleaya cordata* and *Echinacea angustifolia* extracts, contribute synergistically to modulate all the phases involved in the development of OM, from the beginning to the healing phase, thanks to their

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antioxidant, analgesic, anti-inflammatory and antimicrobial properties[10]. Previous studies have shown that SAMITAL® effectively reduces the severity of OM in adult patients, with positive outcomes in terms of pain relief and improved quality of life and a good safety profile with no local or systemic side effects and no systemic absorption[10-12]. A study conducted on 20 Chilean pediatric patients undergoing chemotherapy also showed that SAMITAL® significantly reduced gastrointestinal mucositis grade in younger patients, reducing pain, mucosal erosions, bleeding and dysphagia/feeding impairment, and no related side effects[13].

This study aimed to establish the feasibility of SAMITAL® administration in pediatric patients receiving anticancer treatment to prevent or treat OM by defining the appropriate dose and assessing safety and tolerability. Secondary aims were the evaluation of efficacy, palatability, and absorption of the main active compounds of this botanical formulation.

Patients and Methods

Study Design

This was an open-label, monocentric, prospective feasibility study in children with chemotherapy-induced OM or at high risk of developing OM.

The study was approved by the Italian Medicines Agency (AIFA) and the Ethics Committee of the Azienda Ospedaliera di Padova (Italy) and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines (European Union Drug Regulating Authorities Clinical Trials EUDRACT No. 2015-000386-31) in a tertiary care Pediatric Onco-Hematology Unit from March 2016 to February 2018.

The study enrolled children (aged 2-18 years) with either moderate to severe (grade >2 according to the WHO scale[2]) chemotherapy-related OM (group 1, treatment) or at high risk of developing OM due to intensive chemotherapy, such as high-dose methotrexate, anthracycline or alkylating agents (group 2, prophylaxis). Additional inclusion criteria were a Karnofsky/Lansky performance status score ≥70%, ability to gargle and an estimated survival over 6 months. Exclusion criteria were previous head and neck irradiation, concomitant chronic treatment with steroid or immunosuppressive drugs, pregnancy, and other conditions that may cause OM. Written informed consent from the patient's parents or legal guardians was obtained at the entry into the study.

Treatments

SAMITAL® granules for suspension was donated by Indena SpA, Milan, Italy. Each sachet (1. 5 g) was dissolved in 20 ml drinkable water and administered by 10 ml oral rinse (corresponding to 0.75 g) three-times a day and kept in the mouth for at least 1 minute to allow a slow dissolution and dispersion of the active ingredients in the oral cavity.

SAMITAL® administration started within 3 days from mucositis development (group 1) or on day 1 of a chemotherapy course (group 2). It continued up to OM resolution, patient's withdrawal or after 14 days (only in patients from group 2 who did not develop OM).

Assessments

Patients were followed for approximately 3 weeks after starting SAMITAL® treatment and conducted a follow-up visit 14 days after the end of treatment.

The primary outcome was the feasibility of treatment, defined as children's ability to take SAMITAL®. For each patient, treatment compliance was calculated as the number of doses assumed/number of doses prescribed ×100; good treatment compliance was ≥80%. Compliance was assessed separately in three age groups: 2 to ≤6 years, >6 to ≤12 years and >12 to ≤18 years.

Secondary outcomes included efficacy, palatability and toxicity. SAMITAL® efficacy was assessed as the incidence of mucositis, evaluated at each visit according to the WHO score[2].

SAMITAL® palatability was evaluated according to the Likert method through the following tools: (1) visual analog scale consisting of 6 sad/smiley faces and a score of 0-10 for patients aged 3-7 years; (2) verbal numerical scale with a score 0-10 for patients aged ≥8 years where 0 means "unpleasant taste" and 10 "excellent taste". Palatability was assessed after the first dose and after 1 and 2 weeks of treatment, and mean palatability was calculated for each patient; the evaluation did not apply to patients aged <3 years.

SAMITAL® toxicity was assessed as the occurrence of adverse events, classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). Common adverse events known to be related to chemotherapy were not reported.

Moreover, we evaluated SAMITAL® systemic

absorption by measuring the plasmatic concentration of sanguinarine and dihydrosanguinarine, two benzophenanthridine alkaloids in *Macleaya cordata* extract that may cause adverse effects if systemically absorbed. We used a validated high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS) assay[14], with a lower limit of quantification (LLOQ) of 1 ng/mL and concentration ranging from LLOQ to 200 ng/mL. In total, 2 mL of blood was taken at the following time points: immediately before SAMITAL® administration and 30 minutes (±5), 24 hours (±30 min), 96 hours (±3), and 168 hours (±3) after the administration of the first dose. Blood sample analyses were conducted for the first enrolled patient of each age group for both treatment and prophylaxis groups.

Statistical Analysis

Demographic and clinical data were analyzed descriptively as medians and range. Differences within each study group were evaluated using the Fischer's exact test or Mann-Whitney test. For blood analysis, the following parameters were meant to be calculated in the clinical Protocol by non-compartmental analysis and evaluated as secondary endpoints: Cmax, Tmax and trough levels. A p-value <0.05 was considered statistically significant. Analysis was performed by Kymos Pharma Service SL (Cerdanyola del Vallès, Barcelona, Spagna).

Results

Patient Characteristics

Overall, 27 patients were screened for the study and 18 were enrolled and received at least one dose of SAMITAL®. The main reasons for refusing enrollments were parents' or patients' refusal due to the additional number of medical visits/travels to our center (n=7, most of them adolescents) and difficulties taking oral drugs for the youngest children (n=2). Patients' demographics, disease characteristics, and chemotherapy regimens are presented in Table I.

Table I. Patients' characteristics.

	Group 1 (treatment)	Group 2 (prevention)
Number of patients	6	12
Age (years), mean (range)	12.2 (6.8-16.9)	11.4 (4.6-17.8)
Sex (male/female)	4/2	8/4
Mucositis grade	> 2	0
Disease:		
• Solid tumor:		
ES	0	2
DSRCT	0	1
HB	0	1
OS	3	3
• Hematologic tumor:		
ALBLC	0	1
ALL	1	0
BL	2	3
DLBLC	0	1
• Chemotherapy regimen (n):		
CDDP	0	1
CDDP, DOX	1	1
CP, VCR, ACT-D	0	1
DOX, IR, VCR	0	1
HD IF	0	2
HD IF, ACT-D, VCR	0	1
HD MTX	2	0
HD MTX, IF	0	1
HD MTX, ARA-C, VCR, IF, ETO, DEX	2	2
HD MTX, VCR, CP, DNM, DEX	1	2

ACT-D = Actinomycin D; ALBLC = Anaplastic large B-cell lymphoma; ALL = Acute lymphoblastic leukemia; ARA-C = Cytarabin; BL = Burkitt lymphoma; CDDP = Cisplatin; CP = Cyclophosphamide; DEX = Dexamethasone, DOX = Doxorubicin; DLBCL = Diffuse large B-cell lymphoma; DNM = Daunomicin; DSRCT = Desmoplastic small round cell tumor; ES = Ewing sarcoma; ETO = Etoposide; HB = Hepatoblastoma; HD-IF = High-dose ifosfamide; HD-MTX = High-dose methotrexate; IF = Ifosfamide; IR = Irinotecan; OS = Osteosarcoma; VCR = Vincristine.

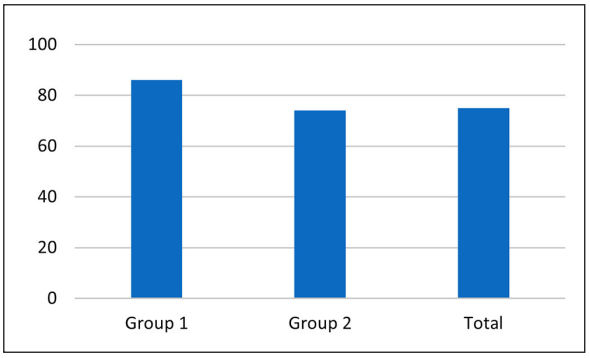

Figure 1. Treatment compliance.

Six patients presented mucositis (grade 2 in four patients and grade 4 in two patients) and were included in group 1, whereas 12 patients at high risk of developing OM were included in group 2. The average age was 12.2 years (range 6.8-16.9) in group 1 and 11.4 years (4.6-17.8) in group 2.

Treatment and Compliance

Overall, 460 doses of SAMITAL® were administered with a median of 30 doses per patient (range 1-50). Treatment compliance ranged from 2 to 100% (median 86% in group 1 and 74% in group 2) (Figure 1). Furthermore, six patients had good compliance, with the consumption of more than 80% of doses, three in group 1 and four in group 2; notably, five out of six were older than 12 years.

Efficacy and Palatability

One child in group 1 interrupted the treatment due to their parents' decision after 4 days (6.8-year-old patient with severe oral pain and extreme difficulty taking oral therapies and consequent low drug compliance, equal to 5%). For all patients, OM resolved after 7-14 days from SAMITAL® start.

Five out of 12 patients in group 2 developed OM, while seven did not develop chemotherapy-induced OM. Among patients who developed OM, one was at high compliance (80%) and four at low compliance (5-76%); however, the difference between the two groups was not statistically significant ($p>0.05$).

The maximum degree of stomatitis of the five patients developing OM in group 2 was grade 2 according to the WHO scale, while in group 1, where patients had active OM at enrolment, it was 2.7. This difference did not reach statistical significance ($p=0.37$) due to the limited number of patients enrolled in the study.

In terms of palatability, the median oral taste evaluation was 4.8 (range 1.0-8.0), without any difference between sex or age groups. The presence of OM did not affect the perception of taste: patients with active OM enrolled in group 1 reported a median taste of 5.6 (range 3.0-8.0), while the median taste in group 2 was 4.3 (1.0-8.0) (Figure 2).

Safety and Absorption Determination of Active Constituents

No SAMITAL®-related side effects were observed or reported by patients or parents recruited in both groups. In total, 23 samples from five patients (two in group 1 and three in group 2) were analyzed with a validated HPLC-MS/MS method to detect the presence of SAMITAL® metabolites in the bloodstream[14]. In all plasma samples tested, sanguinarine and dihydrosanguinarine concentrations were below the LLOQ, showing that SAMITAL® is not absorbed through the oral mucosa.

Discussion

Oral mucositis represents a major problem in the treatment of children with cancer[1]. While different strategies are available to treat or prevent mucositis in adult patients[15], only a few options are available for children. SAMITAL® is a promising botanical drug that may have a role in treating or preventing mucositis in adults and children. In the present study, we tested the feasibility, safety and tolerability of SAMITAL®

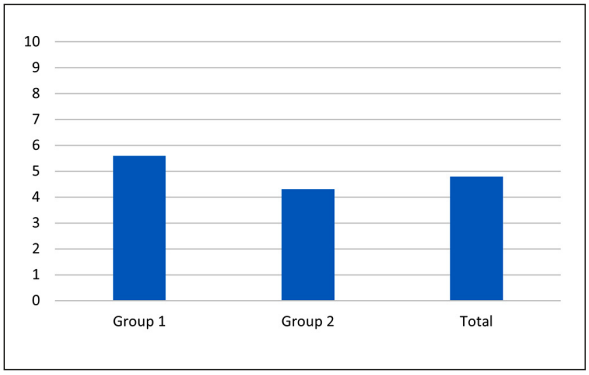

Figure 2. Oral taste evaluation.

administration in 18 pediatric patients treated for cancer as a necessary preliminary step to test its efficacy in the treatment and prophylaxis of OM.

Based on the results of our study, SAMITAL® appears to be safe in children, as no side effects related to its administration were reported. Its action seems to be exclusively topical and local, without diffusion to the bloodstream, as shown by undetectable blood levels of the most important benzophenanthridine alkaloid in the *Macleaya* extract, sanguinarine and its metabolite dihydrosanguinarine.

Despite the positive safety profile, oral administration of the medication was difficult for the young subjects. Two parents declined to participate in the study because their children would have been unable to make an oral rinse with SAMITAL®. Subjects reported both the "bad" taste of SAMITAL®, probably due to the Echinacea bitter taste and its complicated method of administration (mouth rinse for 1 minute three-times a day), resulting in a median low oral taste evaluation (4.8 on a scale of 0-10). These challenges translated into unsatisfying treatment compliance for most patients (66% with compliance <80%), especially among children <12 years of age. The limited compliance in the OM prevention group may also be ascribed to the difficulties of the pediatric population in undergoing prophylactic therapies, while drugs for the treatment of active diseases are generally more accepted.

These results underline the importance of developing specific formulations for oral drugs that target the pediatric population, as currently done for other drugs, such as temozolomide, for which a pediatric formulation is under development to overcome the challenges of oral administration to young patients with glioblastoma or glioma[16]. Indeed, suitable taste and smell are key factors to ensure children's regular assumption of drugs, favoring patient acceptance and compliance[17-19]. In addition to lack of palatability, other factors, such as pain caused by OM, could impair the ability to take oral drugs, especially in younger children.

Given the low compliance to treatment, it is impossible to draw conclusions on the efficacy of SAMITAL® in the treatment and prevention of OM in the pediatric population. However, we noticed that when compliance was good, the incidence of mucositis was very low (only one patient with high compliance developed OM in group 2), and OM degree was, for the most part, low (OM grade 2).

Conclusions

Despite good preliminary results in terms of safety, this study shows that the current formulation of SAMITAL® is only partially suitable for children due to its low palatability. Any further study investigating the potential role of SAMITAL® in the treatment and/or prevention of OM in children with malignancies need an adapted formulation to increase compliance in younger children.

Conflict of Interest

D. Massano, A. Paratella, M.C. Affinita, G.L. De Salvo, G. Bisogno declare no conflict of interest. G. Petrangolini and A. Riva are Indena's employees.

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Availability of Data and Materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study was approved by the Italian Medicines Agency (AIFA) and the Ethics Committee of the Azienda Ospedaliera di Padova (Italy) and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines (European Union Drug Regulating Authorities Clinical Trials EUDRACT No. 2015-000386-31).

Informed Consent

Written informed consent from the patient's parents or legal guardians was obtained at the entry into the study.

Consent for Publication

All patients signed an informed consent to the use of their data for research purposes.

Authors' Contribution

All authors designed the study and wrote the manuscript; D. Massano, A. Paratella, M.C. Affinita, G.L. De Salvo, G. Bisogno analyzed the data; D. Massano, A. Paratella, M.C. Affinita, G. Bisogno performed the study; G. Bisogno, G.L. De Salvo, G. Petrangolini, A. Riva edited the manuscript and gave supervision. All authors have read and agreed to the published version of the manuscript.

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