Bitter ginger (Zingiber zerumbet) for patients with solid tumors with no treatment options: A pilot clinical study

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ABSTRACT

Objectives: We aimed to investigate the role of zerumbone in improving the quality of life and symptom control in cancer patients with no treatment options. Methods: We conducted a pilot, non-randomized, single-center, open prospective, and systematic study on the use of 400 mg of zerumbone twice a day. Results: The study included 35 patients (mean age, 68 years; 64% men), of which 16 completed the eight-week study. The intention-to-treat population showed no significant changes in weight or sleep quality over the eightweek study. Assessments performed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) showed significant improvements in the quality of life in the global (p = 0.072), activity (p = 0.0393), social (p = 0.0001), and emotional (p = 0.0023) dimensions. The Hospital Anxiety and Depression Scale (HADS) questionnaire scores showed significant improvement in anxiety (p = 0.032) and depression (p = 0.021), while the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire scores also indicated a significant improvement (p = 0.001). Bitter ginger showed low toxicity. Conclusions: Bitter ginger showed promising results in improving the quality of life and reducing symptoms of anxiety and depression in the study population. A randomized placebo-controlled study is necessary to confirm these results.

INTRODUCTION

Introduction: Zerumbone is a natural compound found in bitter ginger plants (Zingiber zerumbet) that shows antiproliferative, antioxidant, anti-inflammatory, and analgesic properties. We aimed to investigate the role of zerumbone in improving the quality of life and symptom control in cancer patients with no treatment options

PATIENTS AND METHODS

Study Design and Patients:
This is a pilot, non-randomized, single-center, open prospective study with a convenience sample (ie subjects were includded according to thjeir availability and accessibility). All patients were recruited and followed up at the clinical oncology outpatient clinics of Anchieta Hospital in Sao ˜ Bernardo do Campo and Mario Covas State Hospital in Santo Andr´e , both in S˜ ao Paulo, Brazil, and linked to the ABC Foun dation School of Medicine. We registered the trial on 07/03/ 2023 at ISRCTN (Biomed Central) under the number 4388. The inclusion criteria were age over 18 years, regardless of sex, previously treated advanced solid tumors with no treatment options according to the attending physician, life expectancy of at least two months and preserved renal and liver functions . Pregnant and lactating women were excluded.
Medications:
Zingiber zerumbet (ZZ) rhizomes were collected from Tarum˜ a Mirim, a rural area of Manaus, Amazonas, Brazil. We used 1.40 mL of the extract with starch adjuvant. The ZZ rhizome extract medication was administered in a 400-mg capsule twice a day (every 12 h), every day, according to the medication package insert, for a period of eight weeks.
Stu**dy Procedures**
The protocol involved three visits: the first visit (T = 0) before initiating the treatment, followed by two other visits every four weeks until week eight of treatment. At each visit, the patients underwent anamnesis, clinical examination, blood collection, and specific questionnaire assessments. Blood was collected to evaluate the hematologic and biochemical profiles and thereby detect possible renal and/or hepatic toxicity reactions and to evaluate inflammatory markers (C-reactive protein [CRP], α-acid glycoprotein, erythrocyte sedimentation rate [ESR]).
The included quality of life questionnaires were the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3) the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F, version 4) the Hospital Anxiety and Depression Scale (HADS) and the Chalder Fatigue scale. Sleep quality was assessed using the Brazilian version of the Pittsburgh Sleep Quality Index (PSQI-BR). Adverse events were recorded according to the International Adverse Event Reporting Criteria version 4.0 (CTCAE-V4.0).

RESULTS

The study included 35 patients (mean age, 68 years; 64% men), of which 16 completed the eight-week study. The intention-to-treat population showed no significant changes in weight or sleep quality over the eightweek study. Assessments performed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) showed significant improvements in the quality of life in the global (p = 0.072), activity (p = 0.0393), social (p = 0.0001), and emotional (p = 0.0023) dimensions. The Hospital Anxiety and Depression Scale (HADS) questionnaire scores showed significant improvement in anxiety (p = 0.032) and depression (p = 0.021), while the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire scores also indicated a significant improvement (p = 0.001). Bitter ginger showed low toxicity

Table 3
Toxicity observed during the study and graded according to the CTCAE scale version 4. The most severe type of toxicity that occurred during the study was selected for each patient.

Side effects	CTCAE Grade			
	0 n (%)	1	2	3
Anemia	16 (57,14)	6 (21,43)	4 (14,29)	2 (7,14)
Diarrhea	25 (92,59)	1(3,70)	1(3,70)	0 (0,00)
Anorexia	26(96,30)	1(3,20)	0 (0,00)	0 (0,00)
Nausea	25(92,59)	2(7,41)	0 (0,00)	0 (0,00)
Dyspeptic symptoms	25(92,59)	2(7,41)	0 (0,00)	0 (0,00)
Constipation	26(96,30)	1(3,20)	0 (0,00)	0 (0,00)
Neuropathy	26(96,30)	1(3,20)	0 (0,00)	0 (0,00)
GGT elevation	17(60,71)	5(17,86)	4(14,29)	2(7,14)
Alkaline Phosphatase elevation	25(89,29)	3(10,71)	0 (0,00)	0 (0,00)
AST elevation	27(96,43)	1(3,57)	0 (0,00)	0 (0,00)
ALT elevation	27(96,43)	1(3,57)	0 (0,00)	0 (0,00)
Creatinine elevation	26(92,86)	2(7,14)	0 (0,00)	0 (0,00)
Pain	22(78,57)	4 (14,29)	2(7,14)	0 (0,00)
Petechiae	27(96,43)	1(3,57)	0 (0,00)	0 (0,00)

Table 2
Mean questionnaire scores with their respective standard deviations in parentheses. The upper part of the table refers to the EORTC QLQ-C30 General (GHS) scores and the scores for its physical, role, emotional. cognitive, and social domains. The scores of the other questionnaires used in this study are presented below: Chalder, FACIT-F, PSIQ-BR, HADS-A (anxiety), eHADS-D (depression). The first part of the table refers to the per-protocol analyses of the 16 patients who participated in the three appointments (n = 16), and the second part of the table refers to the intention-to-treat analyses of the 35 patients initially included (n = 35).

EORTC QLQC30	T = 0 (N = 16)	T = 4 (N = 16)	T = 8 (N = 16)	p	T = 0 (N = 35)	T = 4 (N = 35)	T = 8 N = 35)	p
GHS	56,33(32,98)	69,47(27,04)	54,93(35,45)	0132	39,91(32,44)	65,86(35,13)	54,94(35,46)	0.0272
Physical	51,62(29,75)	50,18(19,51)	50,51(29,30)	0947	41,54(29,81)	49,43(32,34)	53,89 (27,06)	0.3065
Role	60,39(37,45)	69,78(33,45)	64,56(38,43)	0679	46,06(35,78)	68,51(34,72)	38,87(65,57)	0,0393
Emotional	63,52(28,19)	84,36(24,70)	89,44(16,50)	0002	60,27(23,75)	81,47(27,20)	84,44(26,70)	0.0023
Cognitive	81,1(21,70)	80,21(20,33)	82,22(22,20)	0805	64,70(30,08)	77,76(20,61)	82,21(22,26)	0.0630
Social	71,14(31,11)	91,68(20,13)	89,99(13,80)	0047	49,00(37,60)	85,18(26,76)	89,99(13,80)	0.0001
CHALDER	12,80(6,09)	11,38(7,09)	12,81(7,20)	0.512	17,12(12,04)	12,72(8,26)	12,81(7,29)	0.0843
FACIT -F	93,07(25,72)	93,81(30,47)	87,25(32,74)	0.514	82,03(26,88)	93,50(29,29)	87,25(32,74)	0.0001
PSQI-BR	7,66(4,73)	6,87(3,46)	7,75(3,99)	0.508	9,45(4,06)	7.05(3,43)	7,75(3,99)	0.0955
HADS A	5,73(3,55)	4,43(3,42)	4,26(2,93)	0.288	7,76(3,89)	4,94(3,98)	4,26(2,93)	0.032
HADS D	5,66(3,03)	5125(4,44)	6,00(3,14)	0.708	8.85(5,20)	5,38(4,40)	6.00(3,14)	0.0217

DISCUSSION

This study had at least two notable limitations. The small number of patients who completed the study reflects a difficulty often encountered in studies involving patients in palliative care, i.e., the loss of patients during follow-up due to death or other reasons. Nevertheless, the significant correlations we found in this study are likely to be repro duced in clinical studies involving a higher number of subjects. Another important limitation is the absence of a control arm in this study using placebo. Without a control arm, we cannot exclude the possibility that the beneficial effects reported here are due to a placebo effect..
These limitations may influ ence the generalizability of our findings. This pilot studies shows that it is feasible to recruit advanced solid tumor cancer patients into a clinical trial evaluating a herbal extract with patient related outcomes (PRO) such as quality of life, anxiety and depression as endpoints. The high drop-out rate that we found is typical of studies with advanced stage cancer patients.

CONCLUSIONS

Bitter ginger showed promising results in improving the quality of life and reducing symptoms of anxiety and depression in the study population. A randomized placebo-controlled study is necessary to confirm these results.
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