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Original

Prevention of Chemotherapy-Induced Neutropenia by Special Honey Intake

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Abstract

Febrile neutropenia is a serious side effect of chemotherapy. Colony-stimulating factors (CSFs) are used for primary and secondary treatment in patients with grade 4 neutropenia. The use of CSFs is expensive and accompanied by side effects. In the current study, Life-Mel Honey (LMH) was administered to prevent neutropenia and to reduce the need for CSFs in patients treated with chemotherapy. Thirty cancer patients receiving chemotherapy for primary or metastatic disease were included. All patients had grade 4 neutropenia and were treated with CSFs. The patients repeated the same chemotherapy schedule, with the addition of LMH for 5 d. Blood count was performed weekly. There was no recurrence of neutropenia after LMH intake and no need for treatment with CSFs in 12 (40%) of patients. Eighteen (60%) patients with LMH developed neutropenia grade 4 and were treated with CSFs ($p = 0.007$). Hemoglobin levels remained >11 g/dL during LMH intake in 19 (64%) patients. Only three (10%) patients had thrombocytopenia. Eight (32%) patients reported improvement in quality of life. The use of LMH in patients who are at high risk of developing neutropenia as a result of chemotherapy decreases the risk of pancytopenia and the need for CSFs. LMH is inexpensive, has no side effects, and is easy to administer.

Key Words: Chemotherapy; cancer patients; hematologic toxicity; honey.

Introduction

Myelosuppression (bone marrow suppression) is the most important toxic side effect of most chemotherapeutic agents and typically is the dose-limiting factor. Death occurring after chemotherapy usually results either from infection related to drug-induced leukopenia or from bleeding related to thrombocytopenia. Chemotherapeutic agents affect the rapidly proliferating pool of blood precursors in the marrow leading to a predictable decrease in the peripheral white blood cell count at approx 7–14 d after the drug is administered, depending on the type and intensity of chemotherapy *(1)*. Incidence of severe infection rises dramatically when the absolute neutrophil count drops below 1000 cells/mm^3. Some possible predictors include a 49% risk of febrile neutropenia (FN) if the absolute lymphocyte count is less than 700/mm^3 *(2)*. In general, FN is treated with immediate hospitalization and the administration of

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intravenous antibiotics *(3)*. In addition to the impact on patients' quality of life, episodes of FN may result in subsequent chemotherapy delays or dose reductions.

Colony-stimulating factors (CSFs) are widely used in adjunct to standard-dose chemotherapy and in febrile neutropenic patients. Routine use of CSFs for primary prophylaxis of FN for any common disease in previously untreated patients can reduce the incidence of FN by as much as 50% *(4)*, but has minimal impact on freedom from disease and overall survival *(5)*. The rationale for secondary CSF administration in patients with a prior episode of FN, preexisting neutropenia due to disease, and a history of neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity is twofold. First, according to the American Society of Clinical Oncology (ASCO) 2000 guidelines *(1)*, this group of patients is most likely to benefit from CSF support, and second, the use of CSF, a relatively expensive treatment with several side effects, would shorten the duration of neutropenia.

This prospective study is based on sporadic cases in which a special kind of honey, Life-Mel Honey (LMH), has improved quality of life and blood count of patients during chemotherapy *(6)*. The aim of the study was to provide prophylactic and protective treatment against neutropenia reducing the need for secondary CSF administration in patients receiving chemotherapy along with LMH.

Statistical Analysis

Differences between means were tested by the Student's t test. p values <0.05 were considered as indicating statistical significance.

Methods

Thirty patients were treated. Eligibility criteria were histologically proven primary or metastatic cancer. Patients were treated with chemotherapy as adjuvant or for metastatic disease. All patients had previously grade 4 (granulocytes count <500 mm^3) neutropenia developed at the same treatment schedule and were treated with CSF. In the next course of chemotherapy, patients received LMH 5 g/d, per os (Express Honey, Tzuf Globus, Israel) for 5 d. Honey was started on the first day of chemotherapy and was taken in the morning on an empty stomach. Honey

Table 1
Medical Plants Used for Nourishing the Bees

Echinacea pallidum	*Taraxacum officinalis*
Uncaria tomentosa	*Chicorium intubus*
Eleutherococcus senticosus	*Vaccinium myrtillis*
Urtica dioica	*Avena sativa*
Calendula officinalis	*Inula helenium*
Trifolium platense	*Melilotus officinalis*
Mellisa officinalis	*Ficus carica*
Morus albus	*Beta vulgaris*
Ribes rubrum	

Table 2
Patient Characteristics Prior to Honey Intake

Characteristic	No. of Patients	%
Total No. of Patients	30	100
Age, yr		
Median	57	
Range	39–76	
Gender		
Male	10	33
Female	20	67
Ethnicity		
Ashkenazi Jews	11	37
Sfaradic Jews	13	43
Arabs	6	20
Site of primary cancer		
Breast	14	47
Lung	7	23
Colon	4	13
Other sites	5	17
Histology		
Adenocarcinoma	11	37
Invasive Ductal Carcinoma	12	40
Malignant lymphoma	2	6
Other histologies	5	17
ECOG PS		
1	10	33
2	14	47
3	6	20
Chronic diseases		
Yes	11	37
No	19	63
Previous treatment		
Surgery	24	80
Chemotherapy	9	30
No chemotherapy	21	70

PS = performance status.

Table 3
Recent Chemotherapy Treatment

Chemotherapy	Number of Patients	
CEF	11	
Taxol + carboplatin	3	
Carboplatin	1	
CPT11 +5FU	4	
Gemzar + carboplatin	4	
Navelbine	2	
CHOP	2	
Taxol	3	
Aim of treatment		
Adjuvant	16	53%
For metastases	10	34%
Neoadjuvant	4	13%

Note = 2 patients with malignant lymphoma were included in the adjuvant group. C, cyclophosphamide; E, epirubicin; F, 5FU; H, adriamycin; O, oncovin; P = prednisone.

Table 4
Blood Count Status Before and After Treatment with Honey

	During chemotherapy Before honey, No. of patients (%)	During chemotherapy with honey, No. of patients (%)
Neutrophils (absolute no.)		
<500/mm^3	30 (100)	18(60)
>500/mm^3	0	12(40) (p = 0.007)
Hemoglobin		
>11 g/dL	8 (27)	19(64) (p = N.S)
10-11g/dL	7 (23)	4(13)
<10 g/dL	15(50)	7(23)
Thrombocytes(absolute no.)		
>90000/mm^3	20(67)	27(90) (p = NS)
<90000/mm^3	10(33)	3(10)

NS; Not significant.

intake was repeated at the beginning of every treatment for 5 d. This honey was produced naturally; the bees were nourished with medicinal plants including *Echinacea pallidum, Uncaria tomentosa, Eleutherococcus senticosus,* and other plants (Table 1). Patients underwent complete blood count at least once a week after every chemotherapy course.

Results

All 30 patients were evaluable. Patient characteristics are outlined in Table 2. Female/male ratio was 2:1. Patients were treated with CEF (cyclophosphamide, epirubicin, 5-FU), paclitaxel and carboplatin, gemcitabine, and single-agent taxanes as adjuvant or treatment for metastatic disease (Table 3). In 16 patients chemotherapy was adjuvant, in 10 it was for treatment of metastatic disease, and in 4 it was used as a neoadjuvant. The median number of honey courses was three (range one to five courses). All patients received LMH. Only patients developing neutropenia under treatment with honey received CSF. Twelve patients (40%) had no neutropenia and no CSF was given; 18 patients (60%) needed CSF because of neutropenia during honey intake (p = 0.007). Hemoglobin levels improved in 19 patients (64%) (p = 0.4) (Table 4). Only three patients (10%) developed thrombocytopenia during honey intake (p = 0.3). Eight patients (32%) reported improvement of quality of life in everyday activities during honey intake.

Discussion

Honey contains various minerals and organic compounds, but is comprised mainly of sugars (about 80%) and water (about 20%) *(7)*. In addition, honey is known to contain a number of enzymes such as diastase, invertase, saccharase, catalase, and glucose oxidase *(8)*. Honey acquires its specific aroma, color, and taste depending on the source from which bees obtain the material for honey production. Apparently, the medicinal and the nutritional properties of honey depend in part on the chemical composition of the flowers from which bees collect nectar. There is a growing interest in alternative and conventional medicine in the honey created by bees nourished by medical plant extracts that are well known. One of these special kinds of honey is LMH *(9)*. The special medical plants used for bees producing LMH are listed in Table 1. The biologically active compounds in these plants are vitamins, alkaloids, organic acids, flavonoids, saponins, tannins, slimes, essential oils, fatty oils, and mineral elements.

Some studies have demonstrated antioxidant activity of honey, particularly an inhibitory effect on

superoxide radical production by xanthine/xanthine oxidase *(10)*. Accumulating evidence supports the assumption that the protective effect of honey against inflammation of whatever source is associated with its antioxidant properties *(10)*.

Neutropenia and resultant infections are potentially life-threatening side effects of cancer chemotherapy. The use of dose-intensive chemotherapeutic regimens makes the management of myelosuppression increasingly important. The use of CSF in patients with established neutropenia after chemotherapy is mostly routine. Chemotherapy can exacerbate the development and progression of anemia in cancer patients. The incidence of transfusion-dependent anemia induced by chemotherapy ranges from 9% to 40%. Treatment with recombinant human erythropoietin (rhEPO) increases hemoglobin levels and reduces transfusion requirements and promote negative side effects.

In the current study LMH was given to patients with severe neutropenia after chemotherapy and to whom CSF was supposed to be given in the next course of the same chemotherapy regimen as a prophylactic treatment. We found this honey to be effective in decreasing the incidence of anemia in 64% of the patients and in decreasing the incidence of severe neutropenia, even though 40% of patients required CSFs. The incidence of thrombocytopenia was also very low. One third of the patients reported improvement of quality of life during honey intake. No side effects were noted following honey intake. LMH was started on the first day of chemotherapy according to the ASCO guidelines, which suggest that starting CSF up to 5 d subsequent to chemotherapy may provide optimal neutrophil recovery *(1)*.

The economic cost of hospitalization for FN is high as is the cost of treating neutropenia with CSFs and the treatment of chemotherapy induced anemia with EPOs. On the other hand, the cost of LMH for preventing neutropenia and anemia is negligible when compared to that of treatment with CSF and EPOs, i.e., about 8% of the cost of CSFs for one course of chemotherapy.

In conclusion, LMH is a very inexpensive, safe, and effective method of preventing chemotherapy-induced pancytopenia. Further studies with larger numbers of patients is planned to confirm our results.

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