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Short Communication

A Simon's two-stage design trial evaluating the potential role of a kind of honey in preventing chemotherapy-hematopoietic toxicities

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ABSTRACT

Background and aim: Hematopoietic toxicities are a serious consequence of myelosuppressive CT that may result in dose reductions, delays or even discontinuation of CT, which, in turn, may compromise patient outcomes. Concerns about tolerability and costs of CSFs are still ongoing, therefore the potential use of supportive therapeutics agents are still of interest.
Experimental procedure: We performed a monocentric, phase II study using Simon's two-stage design. The primary endpoint was the evaluation of the potential clinical benefit of a special kind of honey (Life-Mel Honey) administered prophylactically to reduce the incidence of hematopoietic toxicities following chemotherapy. We have enrolled patients undergoing adjuvant or first-line chemotherapy.
Results and conclusion: From November 2013 to May 2014 (First stage) and from November 2014 to April 2016 (Second stage), 39 patients were enrolled at our Institution. The majority of patients was male (24/39, 61.5%), medium age was 60.4 years (range 34–77 years). The median follow up was 74.5 days (SD +/- 28.5). Overall, the majority of patients could underwent their chemoterapy with a regular schedule (25/39, 64.1%), while 9/39 patients (23.1%) need to delay chemotherapy due to hematological adverse events of various grade. Ten/39 patients (25.6%) had a grade 1 neutrophils count decreased, 56.4% a grade 1 platelets count decrease and 64.1% a grade 1 hemoglobin decrease. Therefore, Life-Mel Honey showed an interesting profile to reduce hematological toxicities. The proportion of responses is sufficiently high to recommend this honey to go to a next step in the clinical trial phase.

1. Introduction

In the last years many new anticancer approaches have been developed. However, antineoplastic CT still has an important role in many human neoplasm and so classical chemotherapy toxicity management has a crucial role. A large retrospective trial has shown that FN during chemotherapy for advanced solid tumours ranged from 13% to 21%.[1] Toxicities management have a direct role in ensuring treatment regular dose intensity and better results.[2,3] CSFs have been shown to reduce the duration and severity of neutropenia and the risk of FN, the American Society of Clinical Oncology (ASCO) has recently updated its clinical practice guidelines about CSF-use.[4] Anyway, concerns about CSFs adverse events and costs are still debated. Based on ASCO guidelines, primary prophylaxis with CSF is recommended in patients who have the 20% risk of developing FN, based on chemotherapy regimen, schedule of administration and patients characteristics (such as age, previous chemotherapy, poor performance status, other comorbidities). For low grade toxicities (G1/G2), who are not typically life threatening but can otherwise lead to treatment discontinuation, no specific treatment is indicated.[5] CT schedules may be correlated to clinical symptoms such as fatigue and

Abbreviations: chemotherapy, (CT); colony-stimulating factors, (CSFs); tyrosine kinase inhibitors, (TKIs); febrile neutropenia, (FN).

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dyspnoea, that often lead to important quality of life reduction.[4,6] The bee-honey Life-Mel is obtained using Zuf Globus Ltd technology, it is naturally produced feeding the bees with various medicinal plants, namely Echinacea pallidum, Uncaria tomentosa, Eleutherococcus senticosus, Ribes rubrum. In Italy Ministry of Health has listed it as a food supplement. In a previous published paper[7] Life-Mel was studied across 30 cancer patients receiving chemotherapy for primary or metastatic disease. Forty percent of the patients had no recurrence of neutropenia nor need for treatment with CSFs. Only three (10%) patients had thrombocytopenia. With this premises we designed a clinical trial using the Simon's Two-Stage Design[8] to assess the potential benefit of administering Life-Mel to prevent myelotoxicity in patients affected by solid neoplasm undergoing CT treatment at low to moderate risk of febrile neutropenia.

2. Methods

The study received specifical approval by the Ethics Committee of the Hospital "AOU Maggiore della Carità" in Novara (CE 61/13). The study was registered in clinical trial.gov (NCT04562922). All patients provided their written informed consent prior to treatment start. This was a monocentric, phase II study according to Simon's two-stage design. Patients were enrolled at the Oncology Department of the Hospital "AOU Maggiore della Carità" in Novara, Italy. The inclusion criteria were age $\geq$18 years old, histologically proven diagnosis of solid neoplasia (to a first overview of the efficacy and tolerability of Lifemel we have decided to enroll various cancer types); patients were treated with adjuvant chemotherapy or for metastatic disease with regimens at low to moderate risk of neutropenia and duration of planned chemotherapy treatment longer than 3 months. The exclusion criteria were known intolerances to honey containing compounds, diabetes, diseases or therapies significantly affecting the neutrophil count, concurrent use of CSF as primary or secondary prophylaxis in the study. Two tea spoons (5 g each) of honey were administered to subjects each day of the chemotherapy treatment. Primary endpoint was to assess the incidence and the grade of neutropenia and secondary endpoint to assess the incidence and the grade of other hematopoietics side effects.

The Simon's two stage minimax design was performed using the following hypothesis: P0 = 50%, the percentage of subjects who did not suffer from neutropenia in the first cycle of treatment (P1) equal to 30%, a type I error = 5% with one tail and power equal to 80%. In the first stage at least 6 responses (grade of neutropenia<=1) in 19 patients enrolled were needed (those patients were considered 'responders') to go the second stage of the study (20 additional patients). Overall, more or equal than 16 responses were considered to render the study suitable to go to a next step in the clinical trial phases.[8] The cut-off has been set according to any grade neutropenia expected at first cycle of low-mild NF risk chemotherapy regimen. Complete blood count has been measured the same day or the day before starting every chemoterapy cycle and at expected nadir (between the 7th and 12th day after chemotherapy depending on CT schedule) in the first 3 months. The adverse events were reported according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). Administration of CSFs was considered an adverse event as well. No long-term follow-up of patients enrolled in the study has been considered for the purposes of the objectives. The survival follow-up was limited to controls after the end of the treatment.

3. Results

Patients were recruited from November 11th, 2013 to May 26th, 2014 (First stage) and from November 26th, 2014 to April 4th, 2016 (Second stage). Totally we have enrolled 39 patients, all patients randomized were enrolled in the trial. In the first stage 19 patients were enrolled. Fourteen/19 patients had not suffered any episodes of hematological toxicity (including all types of the adverse events), while 5/19 showed an episode of adverse event (in detail 1 patient has neutropenia G3, 2 patients had G2 platelet count decreased, 2 patients G2 anemia). According to this, 20 additional patients were included to reach the expected total of 39 patients. Overall, 16/39 (41%) patients had an hematological adverse events of various grade, including the prophylactic administration of growth factors. Baseline clinical characteristics of the 39 patients enrolled are described in Table 1. The majority was male (24/39, 61.5%) patients, medium age was 60.4 years (range 34–77 years). Brain tumours were the most frequent subtype (20/39, 51.3%) followed by head and neck cancers (7/39, 17.9%) and gastrointestinal tumours (7/39, 17.9%). The majority of patients had metastatic disease (25/39, 64.1%) and chemotherapy was administered as first line treatment, while 14/39 (35.9%) patients were in an adjuvant setting. Patients were treated with various chemotherapeutic schedule as shown in Table 1, overall with a low to moderate risk of hematopoietic toxicities. The median follow up during the treatment was 74.5 days (SD +/- 28.5). Overall, the majority of patients could underwent their chemoterapy with a regular schedule (25/39, 64.1%), while 9/39 patients (23.1%) need to delay the chemotherapeutic schedule due to hematological adverse events of various grade and only 1 patient had a discontinuation of the treatment due to haematological unacceptable toxicity, see Table 2 for details. The overall burden of delay or treatment discontinuation was 26 cases among 14 patients. Also, a delay due to neutrophils count decreased (grade>2) was observed in 3 patients. Table 3 shows blood count

Table 1
Baseline clinical characteristics of the patients included in the study.

Gender	N 39 (%)
Male	24 (61.5)
Female	15 (38.5)
Age	
Mean (+/- SD)	60.4 (+/- 12.1)
Min-max range	(34-77)
Site of Primary Tumour	
Head and Neck (oral cavity, oropahrynx, larynx)	7 (17.9)
Gastrointestinal (esophageal/colon-rectum)	7 (17.9)
Liver	1 (2.6)
Pancreas	3 (7.7)
Breast	1 (2.6)
Brain tumours (high grade gliomas)	20 (51.3)
Metastastic tumour	
Yes	25 (64.1)
No	14 (35.9)
Chemotherapy Regimen	
Extreme with carboplatinum AUC5	1 (2.6)
Cisplatin 75mg/mq + taxol 75 mg/mq + weekly cetuximab	2 (5.1)
Weekly carboplatin (AUC2) + weekly cetuximab	2 (5.1)
Weekly cisplatin (40 mg/mq, G1,8 q21) + weekly cetuximab	1 (2.6)
Metronomic cyclophosphamide plus methotrexate	2 (5.1)
Folfiri	2 (2.6)
Folfiri + bevacizumab	1 (2.6)
Folfiri + cetuximab	1 (2.6)
Folfox	2 (5.1)
Fotemustine 80 mg/mq	9 (23.1)
Temozolomide 100 mg/mq	11 (28.2)
Xelox	1 (2.6)
Gemox	1 (2.6)
Gemcitabine + Nab-paclitaxel	3 (7.7)

Table 2
Number of patients with treatment delay or discontinuation.

	N 39
Discontinuation with no adverse hematological effects	3 (7.7%)
Delay with adverse hematological effects	9 (23.1%)
Delay and discontinuation with adverse hematological effects	1 (2.6%)
Delay with adverse hematological effects and discontinuation with no adverse haematological effects	1 (2.6%)
No delay/discontinuation	25 (64.1%)

Table 3
Blood count status and grading with corresponding number of patients affected.

	N of measures	N of patients (%)
Neutrophils (n = 13 patients with at least one measure with grade>=1; n = 6 patients with at least one measure with grade>=2)		
Grade 1	15	10 (25.6)
Grade 2	5	4 (10.2)
Grade 3	4	2 (5.1)
Grade 4	1	1 (2.6)
No events	253	39 (100.0)
Platelets (n = 23 patients with at least one measure with grade>=1; n = 8 patients with at least a measure with grade>=2)		
Grade 1	52	22 (56.4)
Grade 2	5	5 (12.8)
Grade 3	3	2 (5.1)
Grade 4	1	1 (2.6)
No events	217	39 (100.0)
Hemoglobin (n = 26 patients with at least one measure with grade>=1; n = 5 patients with at least one measure with grade>=2)		
Grade 1	112	25 (64.1)
Grade 2	9	5 (12.8)
No events	157	34 (87.2)
White Blood Cells (n = 20 patients with at least one measure with grade>=1; n = 6 patients with at least one measure with grade>=2)		
Grade 1	38	18 (46.1)
Grade 2	7	4 (10.2)
Grade 3	4	3 (7.7)
No events	229	39 (100.0)

status and grading with corresponding number of patients affected. The majority of patients showed grading 1 hematological toxicities, in detail 10/39 patients (25.6%) had a grade 1 neutrophils count decreased, 56.4% a grade 1 platelets count decrease and 64.1% a grade 1 hemoglobin decrease. Across the all measures evaluated, the burden of grade 1 neutrophils decrease was 15/253 measures, 52/217 platelets measures and 112/157 hemoglobin measures.

4. Discussion

Our data showed that 64.1% of our patients could underwent their chemoterapy with a regular schedule. The majority of hematological adverse events was grade G1 according to CTCAEs; 23.1% of patients had to delay the treatment due to hematological toxicities. The availability of CSFs and improvements in antibiotic therapy have changed the management of neutropenia, yet this complication remains a central concern in the delivery and delay of cancer chemotherapy.[4] Predicting the risk of neutropenia, due to many factors depending not only to chemotherapeutic regimen but also to patients-specific characteristics, is not so easy. Therefore the possibility to have more options to prevent neutropenia seems to be interesting for daily clinical practice. Honey contains various minerals and organic compounds and the specific properties of honey depend in part on the chemical composition of the flowers from which bees collect nectar. Several studies are investigating the potential role of honey in the complementary treatment during chemotherapy[9] and a lot of interest is focused on the potential role of supportive care. For example, bee products seem to have a role in the prevention of oral mucositis from chemotherapy or combined chemo-radiation treatment.[10] A previous study has already showed, with this specific kind of honey, that 12/30 patients did not showed neutropenia of any grade with chemotherapy for various metastatic solid tumours.[7] Another study has shown a limitation in FN and hospitalization in 40 children with lymphoblastic leukemia supported with honey during chemotherapy.[11] A chemical analysis of Life-Mel was available before trial started with known plant origin. This honey is rich on flavonoids, terpenoids and oligo-elements. Anyway we are not able to clearly elucidate the underlying mechanism of action that could help in preventing hematological adverse events. A limitation of the study is the fact the all patients were supported with this honey, we don't have a control arm (same chemotherapy schedule without honey feeding). Another limitation is the evaluation of potentially drug-to-drug interactions. The study conducted by Dr. Lee[12] and collegues has shown that the most common type of high-severity potential medication interactions with herbs and supplements involved multivitamins, vitamin D, vitamin E, vitamin C, glucosamine and magnesium. When we started this work we were conscious of the biological active compounds contained in this honey, chemical analysis have been previously reported to clarify this point.[7] Several papers have described drug to drug interactions or food to drug interactions. Multiple sources for interactions were found while combining these drugs: cytochrome interactions, QT prolongation, hepatotoxicity or myelotoxicity.[13] Anyway, the clinical relevance and prevalence of interactions remained unknown due to missing clinical data while only theoretical concepts exist. Combined schedules are more potentially interacting. Drugs most frequently involved in interactions such as ciprofloxacin, fluconazole, pantoprazole and ondansetron are frequently prescribed and administered with cancer therapy. Therefore, clinical detailed evaluation was necessary during the whole study. Overall, 16/39 (41%) patients had an hematological adverse events of various grade. Generally, the two-stage design is employed in Phase II clinical trials to avoid giving patients an ineffective drug. In conclusion, Life-Mel Honey

showed an interesting profile to reduce hematological toxicities. The proportion of responses is sufficiently high to recommend this honey to go to a next step in the clinical trial phase.

Ethics approval and consent to participate

Ethics Committee of the Hospital "AOU Maggiore della Carità" in Novara (CE 61/13). All the patients signed up a written informed consent.

Consent for publication

Provided by all authors.

Availability of data and materials: electronic data

Competing interests: not amenable.

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Highlights of findings and novelties

Potential role for a special honey; supporting hematological events; advanced or adjuvant chemotherapy toxicities.

Authors' contributions

All the authors equally contributed to the trial design and paper writing.

Declaration of competing interest

None.

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