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**Supportive treatment with
herbal yeast preparation
in oncologic systemic therapy**

«Quality of life» field trial in oncologic group practice

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Summary

Many tumor patients undergoing oncologic systemic therapy (chemotherapy, immunotherapy, hormone therapy) request supportive treatment. We conducted a study with an herbal yeast preparation to satisfy this request. The evolution of quality of life under chemotherapy was measured using the EORTC QLQ-C30 questionnaire over several months. A scientific interpretation of the statistical analysis was impossible because of the small sample size. The pilot study showed, however, that supplements, which complement the actual therapy, are feasible, useful and desirable. A new comprehensive study is in preparation (ideally with a randomized placebo group).

Introduction

Through our long-term experience with cancer patients in our group practice we learned time and again that patients would like to actively contribute to their recovery by complementing conventional therapies with supportive treatments. Patients explicitly ask for food supplements. The Swiss Cancer League observed the same need and re-recommends the intake of supplements (1).

As we believe that patients' personal initiatives should generally be supported, we decided to conduct a study to test the effect of a food supplement. For the following reasons we agreed to use Strath*, a product derived from plasmolyzed herbal yeast:

- The product is widely known.
- It has been organically produced under rigidly controlled conditions over decades.

- Studies have been conducted and published in various indications (e.g. radiotherapy (2), ADHD (3), flu (4), microgravity (5) etc.).
- Based on its composition, we do not expect to observe any negative interactions with the actual therapy.

We opted for the use of the internationally recognized EORTC «Quality of Life Questionnaire» QLQ-C30 (6) to evaluate a potential influence of such supportive treatment on the quality of life. Thus, we wanted to create a clean base for its evaluation. This type of additional therapy never had the aim to directly influence the course of the disease. The study has been approved by the responsible ethics commission SPUK Triemli/Waid. The objective of the study was, inter alia, to be able to give well-founded recommendations for the future use of food supplements as supportive treatment in oncologic systemic therapy.

Patients

Patient recruitment was carried out according to the following inclusion criteria:

- Prognostic survival ≥ 4 months
- 18 – 80 years of age
- Karnovsky Index (WHO) $\geq 70\%$
- Patient undergoing oncologic systemic therapy $\geq 75\%$ of study time
- Start of preparation intake during oncologic systemic therapy
- Patient's «informed consent»

Exclusion criteria during the study:

- Missing questionnaires

Between 2003 and 2007, a total of 59 patients, who met the inclusion criteria, were enrolled in the study. Of these, 42 completed their questionnaires during 5 consultations.

Methods

The investigation was originally planned as a self-assigned open-label study where the treatment arm would be compared with a control group in a case-control study. As more than 80% of patients opted for the supplement, however, we had to amend the design and change it into an intra-individual control study with matched pairs. This meant that the performance of participants' individual values had to form the base for the comparison with the scores of the

*) Strath® herbal yeast-based food supplement; Bio-Strath® AG, Mühlebachstrasse 38, CH-8032 Zürich

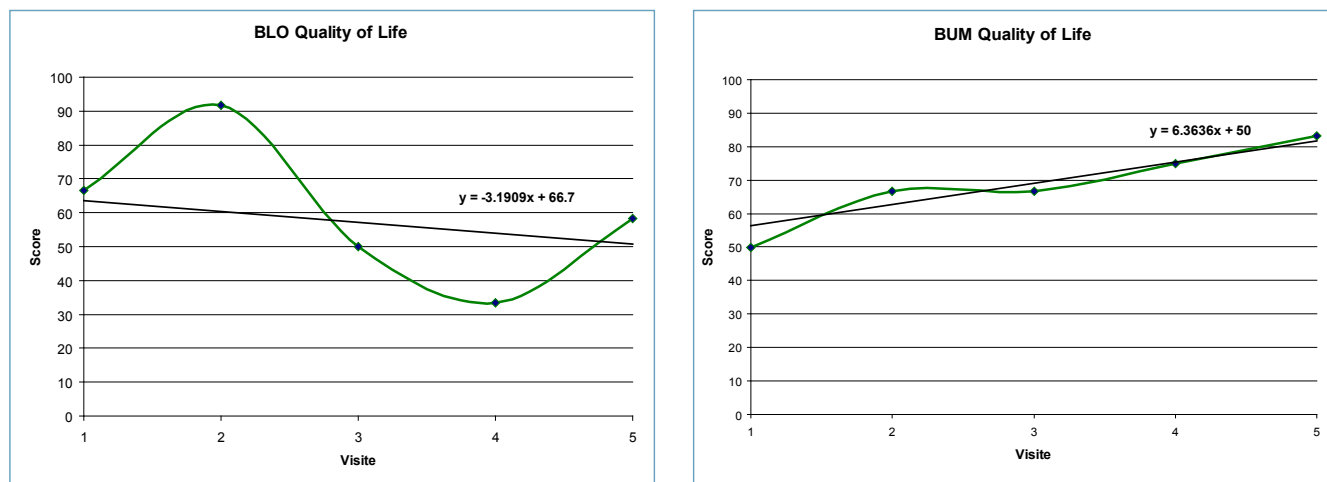


Fig. 1 Example QoL curves with trend calculation (straight line) over 5 consultations. BLO without, BUM with preparation.

matched partners. This pilot study also may serve as basis for a potential follow-up study.

The German version of questionnaire EORTC QLQ-C30, V3.0, developed by the *European Organisation for Research and Treatment of Cancer* (EORTC), was used for the assessment of the quality of life over the course of the study period (5 consultations within 16 ± 1 weeks). It comprises 30 questions, which are subdivided into Global Quality of Life (1 to 7 points), as well as functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning) and symptom scales (nausea/vomiting, pain, fatigue, dyspnoea, sleep disturbances, loss of appetite, constipation, diarrhea, and financial difficulty). The patients were requested to choose between 4 answers: «not at all», «a little», «quite a bit», and «very much». These grades are subsequently converted into a centigrade scale conforming to EORTC specifications, which allow for pooling of single questions or several questions per function or symptom. Higher values for functions signify an improvement of wellbeing, while increased symptom values imply an increased impairment. The EORTC questionnaire is psychometrically robust; it is suitable for various types of tumors and applicable for diverse cultural groups. The analysis is conducted in line with EORTC guidelines. Excel spreadsheets were used for conversion calculations, the pooling of scales and to record the performance over the 5 consultations.

Results

The evaluation of the EORTC questionnaire was conceived as a case-control study. The fact that the subjects were able to choose either the supplement group or the control arm resulted in a marked imbalance of 35:7 in favor of the

supplement group. This disparity and the small sample size rendered sound statistical evaluation impossible.

In order to obtain useful indications from the data of this pilot study we compared the 7 patients not taking the yeast preparation and matched them with the best partners with regard to diagnosis, symptoms, therapy, gender and age. As a result, we had to exclude some participants for the evaluation, who did fulfill the inclusion criteria, but could not be matched with a partner in the control group because of medical or personal characteristics.

Quality of Life (QoL)

In the EORTC questionnaire, patients rated the subjective quality of life in the periods between the consultations on a seven-grade scale from «very bad» to «excellent». These grades were then converted into a centigrade scale conforming to EORTC specifications.

Such progressive values are best represented by a progress curve with a calculated linear gradient. Figure 1 depicts quality-of-life curves for the first pair.

The gradients of the trend lines for all study pairs are represented in table 1. The better value for each matched pair is shaded in gray.

Function scales

In line with the quality-of-life analysis, the data for the individual functions is best represented by a progress curve (fig. 2). Because of the large variations in their courses, the curves are, however, difficult to interpret.

Matching of the subjects*	BLO	BUM	HOO	COM	HUO	JAM	LAO	PRM	LUO	BWM	TOO	MUM	WOO	NEM
Gradient QoL curve	-3.2	6.4	1.5	-0.6	5.4	6.4	-0.3	4.3	-5.2	0.6	2.4	2.4	-4.1	1.4

*) Final letter O: without preparation; final letter M: with preparation

Tab. 1. Gradient of QoL Trend over 5 consultations

The calculation of the linear gradient (analog to QoL) permits us to model the course of the curve purposefully with its highs and lows over the 15 weeks. Table 2 represents the gradients for the 7 pairs. High values signify improved wellbeing. Gray shading depicts the best value for each pair.

The numerical differences of gradients as such do not permit conclusions about medically relevant improvements. As discussed further below, gradient differences of more than 2.5 correspond to the patient perceiving a «marked improvement». Table 3 lists the patients whose grades differ by more than 2.5 from their partner's.

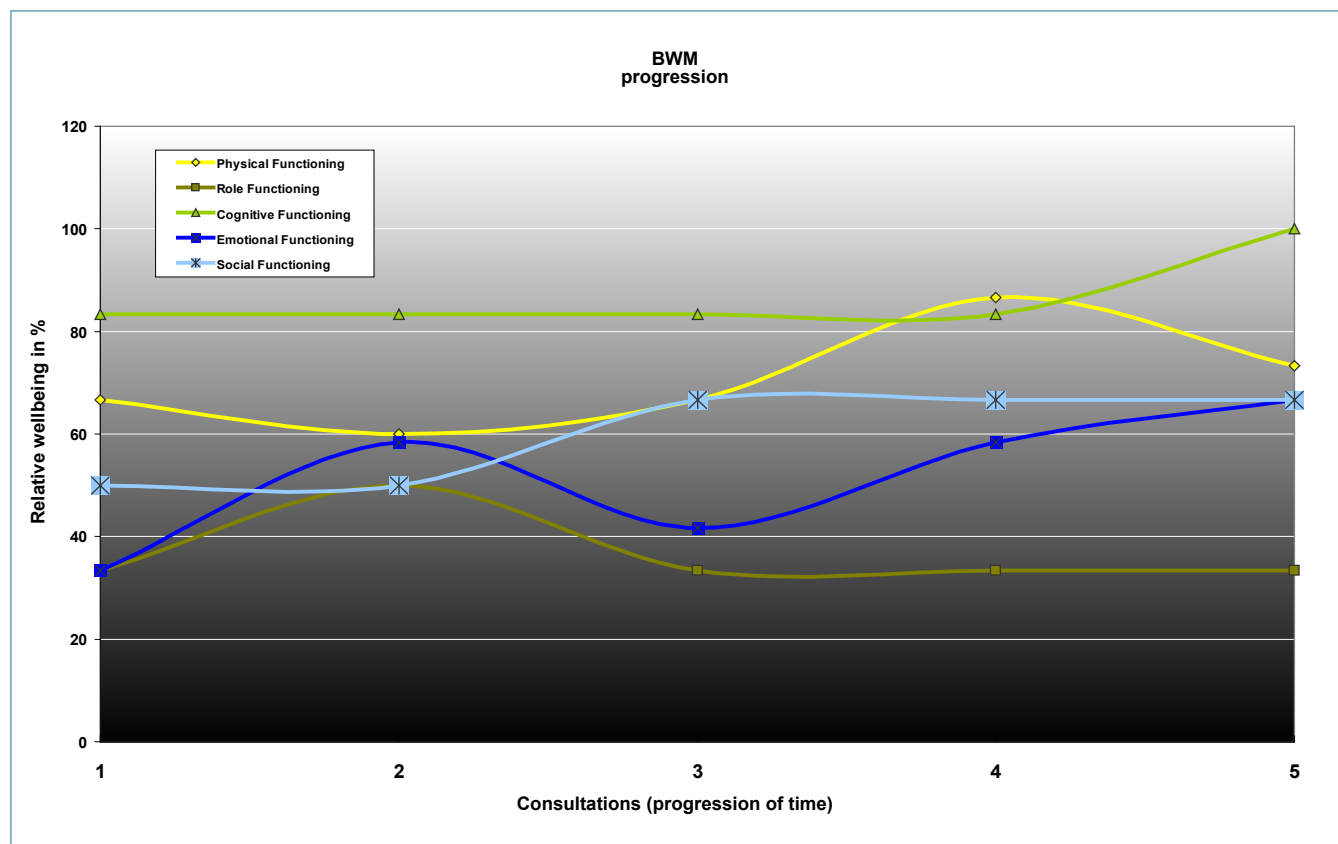


Fig. 2 Example showing all function curves of a subject over 5 consultations

Pairing of subjects	BLO	BUM	HOO	COM	HUO	JAM	LAO	PRM	LUO	BWM	TOO	MUM	WOO	NEM
Physical functioning	5.1	-0.6	0.3	-1.7	1.7	6.2	-0.3	0.3	-0.5	1.7	-3.2	2.3	-0.8	1.1
Role functioning	-1.9	2.9	9.8	-0.4	1.3	15.8	0.2	0	5.5	0.7	2.3	8.3	0	0
Cognitive functioning	-2.6	-0.6	-5.5	1.4	-0.5	-1.7	-2.9	0	4.3	1.6	0	5.1	2.6	-2.7
Emotional functioning	-5.5	-0.4	0.3	2.0	0	-3.5	-3.7	2.0	-2.1	6.3	2.8	11.9	1.9	2.7
Social functioning	-0.1	7.3	-4.8	0.2	2.8	1.0	-2.3	0	0	3.6	-2.0	-1.6	-1.7	0

Table 2. Gradients of trend lines of functions

	Placebo better	Verum better
Physical functioning	1	2
Role functioning	2	3
Cognitive functioning	2	3
Emotional functioning	1	4
Social functioning	0	3

Table 3. Number of patients in the 7 pairs with clinically relevant differences in table 2

Symptom scales

The EORTC questionnaire also assesses physical discomforts. In line with the quality-of-life and the function scales, the symptom scales are evaluated based on the calculation of the linear gradient of the complex curves over the 5 consultations. Lower values represent weaker complaints. The better value of both partners is shaded in gray (table 4).

As with the symptoms, gradient differences are only medically relevant at 2.5 and above. The corresponding evaluation is represented in table 5.

Discussion

We want to state two things: Firstly, a direct influence on the course of the disease has never been a purpose of the study. Secondly, the sample size of the patients evaluated was too small for a strictly scientific statistical analysis.

We were able to show that this kind of study can and should take place at a practice, and that it can be con-

	Placebo better	Verum better
Nausea/Vomiting	1	2
Pain	3	3
Fatigue	0	3
Dyspnoea	3	2
Sleep disturbances	3	4
Loss of appetite	2	4
Constipation	3	2
Diarrhea	2	3
Financial difficulty	1	3

Table 5. Number of patients in the 7 pairs with clinically relevant differences in table 4

ducted at an acceptable expense, not least in view of a follow-up study.

The internationally accepted EORTC questionnaire employs a score to measure the quality of life, human functions and physical symptoms over a certain time period during the course of the disease. This allows for easy calculation of the statistical significance. The figures, however, do not provide evidence about the biological relevance of the changes. Various authors have attempted to reinterpret the numeric scores to obtain a clinically meaningful account of the events: Osoba et al 1998 (7) rated a disparity of between 5 and 10 points to be «slightly better, 10 to 20 points as «marked improvement» and more than 20 points as «very much better». Based on a meta analysis of 14 publications, King 1996 (8) came to the conclusion that a difference in quality-of-life score above 16 points is unequivocally biologically relevant.

Pairing of subjects	BLO	BUM	HOO	COM	HUO	JAM	LAO	PRM	LUO	BUM	TOO	MUM	WOO	NEM
Nausea/Vomiting	0.0	0.0	0.9	0.0	-3.3	0.0	6.4	0.0	4.5	2.4	-7.0	-10.0	0.0	0.0
Pain	0.0	6.1	-0.9	0.6	0.0	-11.8	2.7	0.0	0.0	-11.5	-8.5	-3.0	-5.1	0.0
Fatigue	0.0	-3.8	-1.6	-1.0	-2.8	-4.8	2.4	-2.8	-4.7	-4.3	-7.9	-8.9	3.0	-3.2
Dyspnoea	6.1	8.5	7.3	3.0	0.0	3.0	-8.5	0.0	-3.6	3.0	5.5	-6.1	0.0	0.0
Sleep disturbances	-6.7	-1.2	4.9	0.0	0.0	-3.0	3.0	0.0	0.0	-5.5	-22.4	-13.9	0.0	3.0
Loss of appetite	-3.0	0.0	3.6	0.0	-2.4	-17.0	1.8	0.0	10.3	1.2	3.4	-12.1	-6.1	0.0
Constipation	-11.5	-17.0	-6.1	0.0	-5.4	0.0	0.0	0.0	0.0	0.0	-23.0	1.2	1.2	0.0
Diarrhea	-6.1	1.2	-2.4	8.5	0.0	0.0	4.2	0.0	6.1	-6.7	8.5	-3.0	0.0	0.0
Financial difficulty	0.0	3.0	0.0	-4.2	0.0	0.0	0.0	0.0	0.0	-7.3	0.0	-8.5	0.0	0.0

Table 4. Improvement or worsening of physical discomfort based on gradient values

With regard to the clinical conclusiveness of the gradient, we calculated and ascertained in consideration of Osoba and King that a variation in the gradient of at least 2.5 signifies the assertion of «marked improvement» (15 points). For the difference between the matched partners we attained 2.5 as threshold value for a well-founded assertion.

Published EORTC studies tend to compare two points in time, which makes statistical evaluation relatively easy. As we are mainly interested in quality-of-life evolution, statistical analysis becomes much more complex. We tried to mathematically compare the curves of the means at every point in time, the first mean with the mean of the following consultation or the average of the first two consultations with the average of the last three consultations. We came to the conclusion that the linear gradient for each individual curve represented the best comparison criterion and provided the most conclusive results.

The sample size the results are based on turned out to be too small for sound medical statistics because the subjects were able to freely choose the study group. For that reason, we will not comment further or interpret the results we ascertained.

Qualitatively, the study, however, showed that we were able to satisfy a need that is felt by a majority of patients.

Very positive, but not unexpected, was the finding, that patients taking supportive treatment with an herbal yeast preparation did not objectively or subjectively experience any undesirable side effects.

Our explorative study offers indications that make the null hypothesis that food supplements do not improve quality of life appear most likely not valid. We reckon that the intake of supplements has shown to have a posi-

tive effect in some aspects and can be recommended for patients undergoing oncologic systemic therapy.

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