Homeopathy in cancer (HINC)

Study protocol

Prospective, randomized, placebo-controlled, double-blind, three-arm multicenter study evaluating survival and quality of life in patients with non small-cell lung carcinoma with or without “add-on” homeopathy

Acronym: HINC

PROJECT- OBJECTIVES & AIMS:

We want to test for

1. Survival time

2. Quality of Life (QoL)

3. Subjective well-being

of conventionally treated cancer patients, with patients who receive an “add-on” homeopathic treatment and placebo homeopathic treatment in a double blind randomized prospective non interventional three-arm clinical trial. In addition, we want to investigate homeopathy as a system versus homeopathy as a medicine.

PROPOSER

Partner	Contact	Location	Profession / Role
Proposer Partner 1	Michael Frass	AKH KIM-1	Project leader

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GERMAN ABSTRACT - PROJECT SUMMARY

Prospektive, randomisierte, placebo-kontrollierte, doppel-blinde, dreiarmige multicenter Studie zur Evaluation des Überlebens und der Lebensqualität von PatientInnen mit nicht-kleinzelligem Lungenkarzinom mit oder ohne additive Homöopathie.

Homöopathie wird kontroversiell diskutiert. Eine frühere Studie hat gezeigt, dass eine begleitende homöopathische Behandlung Lebensqualität und subjektives Befinden im Vergleich zu nicht homöopathisch behandelten PatientInnen positiv beeinflusst (Frass M et al. Additional treatment with homeopathy in cancer patients. Third European Congress for Integrative Medicine, Berlin 2010). Das Ziel dieser prospektiven randomisierten placebo-kontrollierten, doppelblinden, drei-armigen multizentrischen Studie ist es daher, bei PatientInnen mit nicht kleinzelligen Lungenkarzinomen (NSCLC) Stadium IV sowohl die Überlebenszeit als auch die Lebensqualität und subjektives Befinden von PatientInnen mit oder ohne homöopathische Begleittherapie zu untersuchen. Eine dritte Gruppe wird ohne jegliche homöopathische Intervention hinsichtlich des Überlebens beobachtet und dient als Kontrollgruppe. Damit wird die Homöopathie als System untersucht um jegliche psychosomatische Interaktion auszuschließen.

ENGLISH ABSTRACT

Traditionally, homeopathy is discussed controversially. A previous study showed that “add”-on homeopathic treatment of tumor patients influences life quality and subjective well-being positively as compared to patients without add-on homeopathy (Frass M et al. Additional treatment with homeopathy in cancer patients. Third European Congress for Integrative Medicine, Berlin 2010). The aim of the present prospective randomized, placebo-controlled, open-label double-blind, three-armed multicenter study is to evaluate survival as well as quality of life (QoL) and subjective well-being in add-on homeopathically treated patients with non small-cell lung carcinoma (NSCLC) IV. A third group without any homeopathic intervention is observed regarding survival and serves as a second control group. Thereby, in our project homeopathy is also investigated as a system in order to rule out any psychosomatic intervention.

2 BACKGROUND

2.1 CANCER

Non-small cell lung cancer (NSCLC) stage IV – Zöchbauer-Müller

PREVALENCE – DIAGNOSIS – TREATMENT

NSCLC comprises about 85% of all lung cancers. About 40% of patients with NSCLC are diagnosed with stage IV disease by image guided methods. These patients are treated with first-line chemotherapy.

First-line chemotherapy of advanced NSCLC consists of platinum-based doublets containing third generation anticancer drugs. Chemotherapy in addition to best supportive care improves survival with an absolute gain of approximately 10% at 1 year (NSCLC Collaborative Group JCO 2008, 26, 4617).

Median survival is about 10.1 months (Pirker R, et al; FLEX Study Team. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009 2;373:1525-31) and 1-year survival rates are about 40%.

2.2 POTENTIAL OF HOMEOPATHY IN CANCER PATIENTS

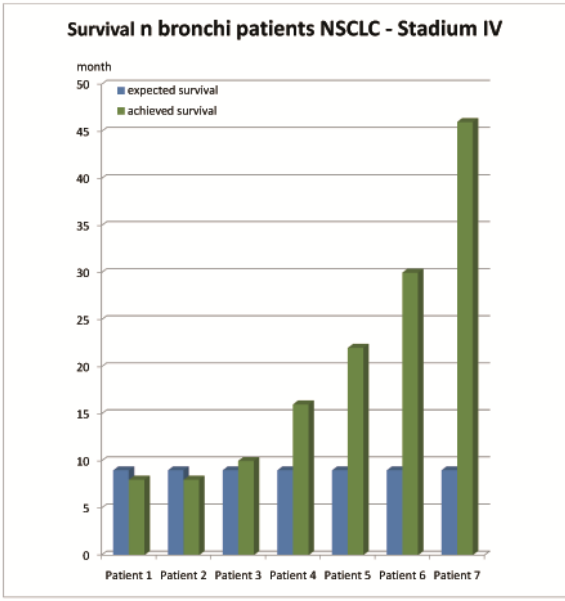
The underlying work hypothesis of classical homeopathy is to apply a remedy which simulates symptoms as close as possible as the symptoms a sick person. It is claimed that homeopathy strengthens the body by constitutional support. In cancer patients, additional features might be of interest, such as alleviating side effects of conventional chemotherapy, radiation as well as surgical therapy; ameliorating secondary diseases; and improving life quality.

In principle, the additive homeopathic treatment of cancer patients is not different from treatment of patients suffering from various other diseases.

A recent study describes the process and outcome of a selected case series review through the NCI BCS Program. The results of the review were deemed to be sufficient to warrant NCI initiated prospective research follow-up in the form of an observational study (Banerji P, Campbell D, Banerji P. Cancer patients treated with the Banerji protocols utilizing homoeopathic medicine: A Best Case Series Program of the National Cancer Institute. USA Oncology Reports 20: 69-74, 2008). Two patients with lung carcinoma showed complete remission without conventional therapy.

Dario Spinedi and Jens Wurster have published a book describing the use of homeopathy in severe cancer cases (Jens Wurster: Homeopathic treatment and cure of cancer and metastasized carcinoma, Peter Irl Verlag, 2010).

A previous study suggests a possible positive effect of “add-on” homeopathic treatment with regard to life quality and subjective well-being in patients suffering from various tumor entities and stages (Frass M et al. Additional treatment with homeopathy in cancer patients. Third European Congress for Integrative Medicine, Berlin 2010). Three questionnaires, the EORTC QLQ-C30, the SF-36, as well as a specific new validated questionnaire were completed by the patients at the first appointment as well as at each follow-up. The questionnaires had to be completed at least three times to evaluate a possible influence of homeopathic medication. A colleague mentioned that she has the impression that cancer patients treated additively with homeopathy live longer. Therefore, we performed a thesis evaluating survival. To our surprise, patients lived much longer than expected:



The aim of the proposed study is to evaluate whether survival as well as life quality and subjective well-being might be influenced by homeopathy in patients suffering from non-small cell lung carcinoma (NSCLC) stage IV.

3 AIM HYPOTHESIS

We aim to investigate the validity of our previous results (Frass M et al. Additional treatment with homeopathy in cancer patients. Third European Congress for Integrative Medicine, Berlin 2010) in a randomized prospective, placebo-controlled, double-blind, three-arm multicenter controlled evaluation of survival as well as of QoL by questionnaires in patients with advanced NSCLC. We plan to compare the treatment outcome (survival and QoL) in tumor patients, receiving verum or placebo homeopathic treatment. A third group without any homeopathic intervention is observed regarding survival and serves as non-interventional control group. Thereby, homeopathy is also investigated as a system to rule out any psychosomatic interaction.

The null hypothesis is that “add-on” homeopathic treatment does not create a benefit with regard to survival for NSCLC patients. In addition we evaluate Quality of Life (QoL).

4 OVERALL TRIAL DESCRIPTION

In a collaboration with (see names of the interdisciplinary project team members under item “6” of this document)

1.) specialists for conventional tumor treatment and

2.) trained homeopaths, we want to explore the possible effects of “add-on” homeopathic treatment in cancer patients.

- we will perform a prospective, randomized, placebo-controlled, double-blind, multicenter evaluation of questionnaires to compare the three arms (with placebo and with verum add-on homeopathic treatment; patients with standard care without any homeopathic intervention)
- The study parameters will be 1) quality of life and subjective well-being from time of diagnosis, 2) patient survival
- Considering the patient frequency at the proposer’s site we foresee project duration of about seven years: 300 patients will be recruited. An interim analysis with non-binding stopping for futility option will be performed after the observation of 140 events.

5 METHODOLOGY

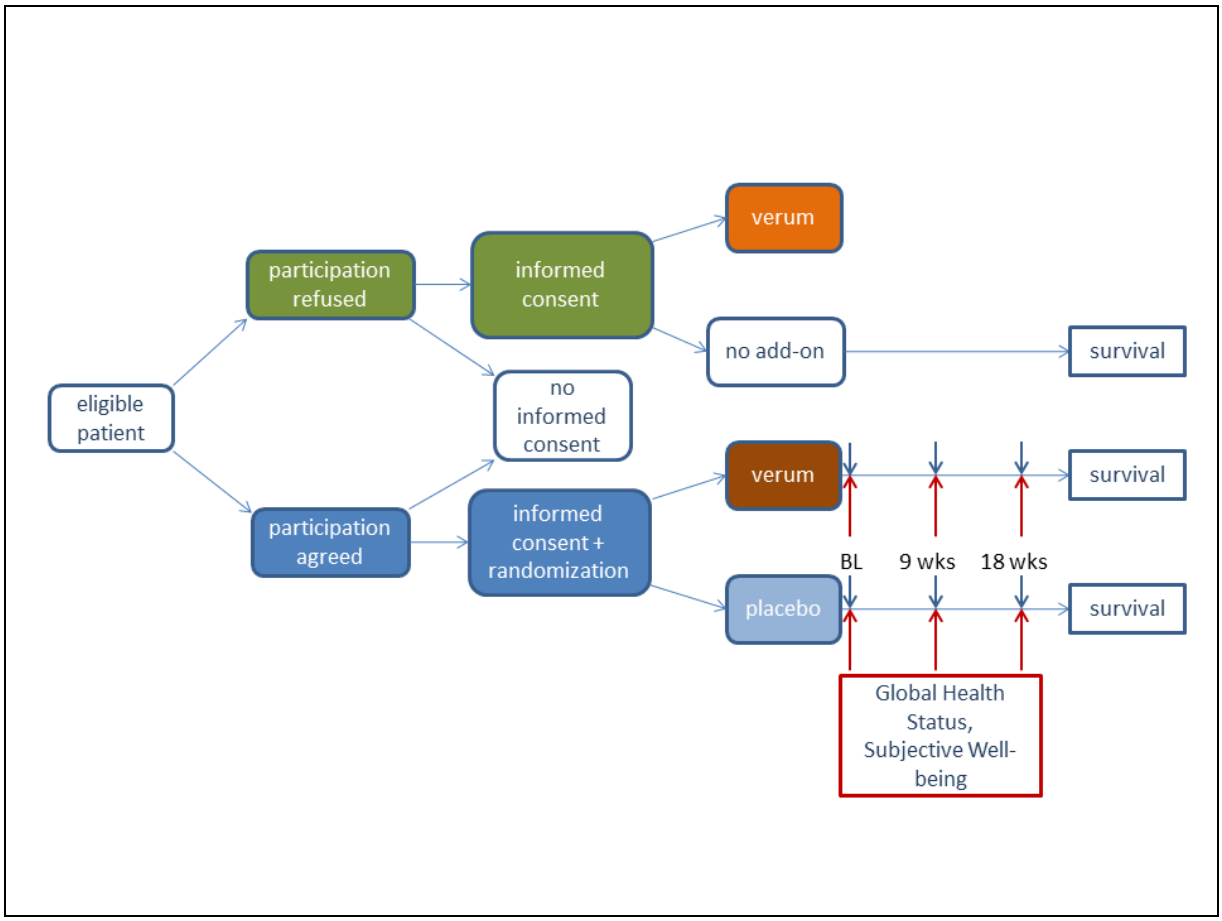
5.1 CLINICAL TRIAL

5.1.1 Patient recruitment

The newly diagnosed patients are recruited at the participating centers. Inclusion criteria are: Patients older than 18 years suffering from NSCLC stage Ivor IIIB, IIIC diagnosed within the last 8 weeks. Exclusion criteria are: Patients not willing to sign informed consent and pregnant patients; major surgery within 4 weeks or chest irradiation within 12 weeks before study entry, active infection, and symptomatic peripheral neuropathy; intake of homeopathic remedies except those prescribed within the study; intake of Schüssler salts, complex remedies, Chinese herbs; patients not willing to take the homeopathic remedies prescribed during the study. Following agreement to participate and signature on the informed consent form, the patient completes the three questionnaires as described below. Then, a classical homeopathic anamnesis is taken by the homeopathic physician. Following the anamnesis, a homeopathic repertorisation is performed. Finally, the physician explains the patient how to take the prescribed remedies without giving the names of the remedies to them. Then, the physician prescribes the remedies and telefaxes the prescription on a special form, or emails them to the pharmacy. At the pharmacy, the following stratification criteria are entered into a randomization program (Randomizer© Medical University Graz, Austria) for permuted blocks randomization: age of patient, sex, Karnofsky index, and center. The pharmacy now prepares the respective remedies and sends them blinded directly to the patient. This design insures the double–blind nature of the study as it creates a system where the treating physician is in no position to know which patient receives the verum or the placebo homeopathic medicine.

Patients declining to participate undergo standard care alone without homeopathic intervention/treatment (verum or placebo). This group serves as control group without homeopathy as a third arm of the study. This third arm is necessary to answer the question about the difference between medication and the homeopathic intervention itself (Brien S, Lachance L, Prescott P, McDermott C, Lewith G. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled clinical trial. Rheumatology (Oxford). 2011;50:1070-82). Otherwise, one could hypothesize that the act of homeopathic intervention itself might have a significant effect which could be valuable to these terminal patients, yet our study design rules out such a scenario. For these non-participating patients, only survival time will be recorded, however, no questionnaires are completed.

We assume that the number of patients who refuse to be randomized but chose to undergo homeopathy is very low. Therefore, this arm is not considered any further in this study.



Sample size calculation is based on a significance level of 5% and a median survival of 10.1 months for group 1 (without homeopathic add-on), see Pirker (Lancet, 2009). Furthermore, 60 months recruitment period with a 24 months observational period in each patient is planned. Under these assumptions 300 patients (corresponding to an average accrual rate of 5 patients per month) give 85% power to detect a difference of 10.1 vs. 14.5 months.

Since the trial duration is quite long a two-stage design (O'Brien-Fleming type with equal information rates) with an interim analysis is planned using the above assumptions (Addplan, Version 6.0.8): An interim Analysis with non-binding stopping for futility option will be performed after the observation of 140 events (which is expected to be after 22 months under the above assumptions). Early rejection of the null hypothesis at interim is tested at a two-sided significance level of 0.0052, the null hypothesis is accepted at interim (stopping for futility) if the p-value exceeds 0.5. The two-sided significance level for the second stage is 0.048. Maximum

sample size is estimated to be 302 (corresponding to 279 events), expected (average) number of events is 209 under the null hypothesis and 242 under the alternative.

5.1.2 Questionnaires

For the documentation of the quality of life, the QLQ-C30, the SF-36 and a subjective well-being questionnaire will be used at any visit.

5.1.3 Evaluation of patients' survival

Overall survival is the most objective end-point to be used in a clinical cancer study. Patients' survival is recorded during control visits every 2 to 3 months. In addition, patients agree that one or two persons named by him/her may be contacted for study-specific follow-up clarification of the end-points.

5.2 PARAMETER ANALYSIS

The obtained and recorded raw data from this prospective, randomized, placebo-controlled, double-blind, multicenter 3 arms trial will be used to compare between the two randomized groups with regard to the following outcomes:

- primary outcome at 9 and 18 weeks versus base line:
    - QoL evaluated as Global Health Status
    - EORTC-QLQ-C30 (remaining dimensions)
    - SF-36
    - subjective well-being
- secondary outcome: overall survival time after 2 years observation from diagnosis
- side effects
- If study support enables a study nurse, analysis of antiemetic medication will be included
- The non-randomized group without any add-on will be compared to each of the randomized groups with respect to overall survival (no other outcomes are measured for these patients). These comparisons are only of exploratory character due to the high selectivity of the non-randomized group. The confirmatory analysis is restricted to the two randomized groups.

5.2.1 Statistics

- Efficacy will be assessed in the intention-to-treat sample, which includes all randomized patients. Safety will be assessed in the as-treated sample, which includes all randomized

patients who have received at least one dose of the assigned therapy. Randomized patients receive at least three Q-potencies of the assigned homeopathic therapy.

- IBM SPSS statistics 25.0 will be used for all analyses, ?=5% (two-sided). Frequencies (n) and valid percentage will be used for reporting dichotomous and categorical data; minimum and maximum (range), mean and standard deviation for continuous variables. Group comparisons for 2x2 crosstabs will be calculated via Fisher's exact test, those for larger crosstabs via X^2-test. Univariate comparisons of two group means will be done with t-test for homogenous respectively heterogenous variances (homogeneity tested by Levene's test), comparisons of two group medians with Mann-Whitney-U-tests, univariate comparisons of three group means by analyses of variances (ANOVA) and prior testing of homogeneity of variances and co-variances (Levene test) and pairwise post hoc Scheffé tests. Multivariate comparison of means for multiple assessment scales of psychological tests will be done via General Linear Model (multivariate analyses of variances with preceding test for homogeneity of variances and covariances via Box-M-Test) respectively via General logistic model for repeated measurements (with preceding test for homogeneity of variances and covariances via Box-M-Test test estimation: Wilk's ?). Kaplan-Meier curves will be used to graphically display the survival comparison between the groups, Log-Rank-test (Mantel-Cox; two-sided) will be used to assess group differences in survival, estimates of mean survival time in days (hazard ratios) and 95% CIs will be given overall and as well for each study group. Survival rates for study groups will be given in %, Wilcoxon (Gehan) Statistic is used for overall and pairwise comparison of rates.
- The obtained and recorded raw data from this prospective, randomized, placebo-controlled, double-blind, multicenter 3-arms trial will be used to compare between the two randomized groups with regard to the following outcomes:
- Primary outcome: QoL as evaluated as global health status and subjective well-being at 18 weeks (third visit after second prescription) versus base line (EORTC-QLQ-C30 remaining dimensions; SF-36; subjective well-being)[25] using the EORTC QLQ-C30-scoring manual.
- Secondary outcome: overall survival time.
- All three groups will be compared overall and pair-wise to each other with respect to overall survival (no other outcomes will be measured for these patients).

6 INTERDISCIPLINARY PROJECT TEAM MEMBERS

Partner	Person	Initials	Role
KIM-1	Michael Frass, MD	MF	Internal physician, Homeopath
KIM-1	Sabine Zöchbauer-Müller, MD	SZM	Oncologist, NSCLC
Otto-Wagner-Hospital Vienna	Otto Burghuber, MD	OB	Pulmonologist-Oncologist
Maria Treu Pharmacy	Ilse Muchitsch, PhD pharm	IM	Preparation of study substances, handling of placebo and verum
Dept Internal Medicine Hospital Lienz	Peter Lechleitner, MD	PL	Oncologist Homeopath
Center for Medical Statistics, Informatics, and Intelligent Systems	Andreas Gleiß, PhD	AG	Biostatistician

7 PROJECT RESSOURCES

7.1 PARTNERSHIP

The project benefits from the synergies of five specialized teams, which are coordinated by the project leader. The realization of the work packages is within the scope of each participating partner. The equipment and facilities are available at the partner’s institution. We request only the required additional man-power and project specific consumables for the study specific documentation work.

As each team is well experienced and equipped for the planned work, no particular investments in hardware or training of personnel is necessary.

7.2 RELATION TO OTHER PROJECTS

- The project largely benefits from work done previously.
- Each partners' project role is within the key competence of the according partner.

8 POST PROJECT ACTIVITIES / RESULT EXPLOITATION

We envision various ways of data exploitation

Publish the results in:

- National and international meetings and
- Peer reviewed journals
- Web publications
- Participation on "science days" to reach the interested public

9 TIMETABLE OVERVIEW

1st year	2nd year	3rd year	4th year	5th year	6th year	7rth year
Recruiting + treating patients	Recruiting + treating patients	Recruiting + treating patients	Recruiting + treating patients	Recruiting + treating patients	Treating patients	Treating patients Statistical evaluation

10 WORK PLAN OVERVIEW

Preparatory work [informed consent sheets; case report form (CRF); envelopes for randomization]: March to April 2012

Distribution and collection of questionnaires: May 2012 – April 2018

Statistical evaluation: May 2019

11 EFFECT ON IMPROVEMENT OF CLINICAL PRACTICE AND TREATMENT OF PATIENTS

If the outcome of the study reveals an improvement of survival, QoL, and subjective well-being it will have a severe impact on the future clinical practice for cancer patients in a way as homeopathy is a low-cost treatment and debits the public social security system to a minor degree.

In addition the acceptance of homeopathy in a clinical environment increases the trust and confidence of those therapists, who consider the additive treatment as a valuable asset in their own specialized branch.

Further on, a positive result of the study might invite potential investors and companies to support future research projects.

12 STUDY RATIONALE

Improvement of survival, quality of life, and subjective well-being is the major endpoint of the trial.

13 ETHICAL ASPECTS OF THE PROJECT

The advantage of potentiated homeopathic remedies is that the dosage does not affect the metabolism of the patient and does not cause interaction with conventional treatment of the involved cancer patients.

14 COMMON RULES AND REGULATIONS

The study is conducted according to GCP regulations installed at the Medical University of Vienna. The study follows the Declaration of Helsinki.

14.1 NATIONAL AND INTERNATIONAL COOPERATION

This project is a nationally coordinated and financially approved study within Austria and Germany under the involvement of the general Hospital of Vienna in close cooperation with the other clinics.

14.2 HUMAN RESOURCES

In total thirteen doctors and scientific staff members are involved.

15 RESEARCH VENUE

Research is performed at the

- General Hospital of Vienna, Austria
- Otto Wagner Hospital, Vienna, Austria
- the Hospital of Lienz, Tirol, Austria; and
- Elisabethinenspital, Department of Medicine, Linz, Austria

The personnel involved works in the outpatient units of the respective hospitals.