The effect on quality of life of vitamin D administration for advanced cancer treatment (VIDAFACT study): protocol of a randomised controlled trial

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ABSTRACT

Introduction: Vitamin D is related to resistance to chronic diseases, physiological parameters and functional measures. All of these relationships underscore the potential benefits of cholecalciferol or D3 (nutritional vitamin D) in cancer. This is the first study designed to obtain conclusive evidence on the effect of cholecalciferol in advanced patients with cancer. The main goal is to assess its effects on the patient’s perceived quality of life. Cholecalciferol’s impact on fatigue and physical performance, as well as its cost utility, will also be assessed.

Methods and analysis: A randomised triple-blind phase II/III placebo-controlled multicentre trial has been designed. Patients satisfying the inclusion and exclusion criteria will be randomly assigned to receive cholecalciferol or placebo. Eligible patients will be adults with a locally advanced or metastatic or inoperable solid cancer in palliative care, who have given signed informed consent and have matched inclusion and exclusion criteria. The randomisation will be based on a computer-generated procedure and centralised by the pharmacy service of the coordinating centre. The assigned treatment will be administered by the hospital’s pharmacy to conceal group allocation for each individual, which can be appropriately assessed by currently available questionnaires which measure the patient’s perception of the impact of fatigue on his/her quality of life.

INTRODUCTION

Background and rationale
Cancer-related fatigue is the most common symptom in patients in palliative care with an overall prevalence of 90% at terminal stages. However, cancer-related fatigue cannot be easily diagnosed, since it may be masked by pain, dyspnoea or nausea. It often becomes apparent once it compromises basic daily life activities. Additionally, there are also subjective, psychological and emotional components of the impact of lack of strength on each individual, which can be appropriately assessed by currently available questionnaires which measure the patient’s perception of the impact of fatigue on his/her quality of life.

The pathogenesis of cancer-related fatigue is multicausal and involves physiological and biochemical disorders directly associated with tumour progression, severe adverse effects resulting from cancer treatment, as well as physical and psychological stress, anaemia, lack of exercise, chronic pain and severe uncontrolled symptoms.

At present, a variety of interventions have been studied with reportedly small but significant benefits such as drug therapy, which are not free of adverse effects. Psychosocial and physical interventions on fatigue intensity are also available for patients with cancer. However, in patients in palliative care, recommendations for therapy are scarce. Functional rehabilitation should be
tailored to each patient to help maintain a relatively active daily life. The goal is not to recover a specific level of activity, but to maintain physical endurance so that rest or inactivity will not reduce muscle reserve.

Vitamin D is a fat-soluble vitamin present in only a few foods, but which can be obtained from sun exposure and supplements in its biologically inert form. It must undergo two hydroxylations in the body for activation. First, the liver converts vitamin D to 25-hydroxyvitamin D (25(OH)D), and afterwards the physiologically active 1,25-dihydroxyvitamin D (1,25(OH)2D) is produced mainly by the kidneys.

A recently published review supports numerous reports delineating the multiple mechanisms underlying vitamin D prosurvival actions experimented with at the laboratory. Their findings show that vitamin D deficiency results in a defective control of: (1) Cell growth causing hyperproliferative disorders, genomic instability, Tumour necrosis factor Alpha Converting Enzyme (TACE)-driven metastasis, exacerbated growth and immune escape; and accelerated progression of cancer lesions; (2) DNA repair mechanisms causing age-associated disorders and resistance to therapy in cancer; (3) Muscular weakness and impaired neuromuscular function; (4) Musculoskeletal pain derived from cancer treatment; (5) The immune system causing increased antigenicity in antigen presenting cells, reduced content of T-regulatory lymphocytes, systemic inflammation and multiple organ damage, as well as a higher propensity for autoimmune disorders; (6) The integrity of the FGF23/klotho responsible for the antiageing properties of klotho in the kidneys, in protecting the vasculature from atheromatosis and calcification, and as a tumour suppressor and protector from the onset of resistance in cancer treatment; (7) The renin-angiotensin system to prevent hypertension, renal and cardiovascular damage due to excessive oxidative stress; (8) Acquisition of atherothrombotic phenotype of circulating monocytes-macrophages and increased severity of atherosclerotic lesions; (9) Podocyte function to protect from proteinuria and proteinuria-induced cardiovascular lesions.

When no curable treatment is possible, palliative care is directed towards minimising symptoms, relieving suffering and bringing patients to the best possible health-related quality of life (HRQoL). Avoiding the toxicity associated with some palliative treatments is a must in these patients. There is an urgent need to develop new interventions in this population based on current evidence, namely: (1) The strong epidemiological association between vitamin D deficiency and the high risk of mortality from all causes in the general population and specifically from cancer; (2) The high frequency of vitamin D deficiency in patients with cancer, estimated to be between 47% and 88%; (3) The anticancer, antiaging, antipain, immunomodulatory and the protective renal, cardiovascular and neuromuscular properties of a normal vitamin D status; and (4) The significant 11% reduction in all cause mortality estimated for D3 by combining all randomised controlled trials. We present a clinical trial designed to obtain, for the first time, evidence-based recommendations on the efficacy of vitamin D3 supplementation, a safe, non-costly therapeutic strategy, in improving physical performance, decreasing fatigue and increasing HRQoL in patients with advanced cancer in palliative care.

**OBJECTIVES**

The primary objective of this study is to evaluate the efficacy of the administration of vitamin D3 to enhance patient-reported HRQoL.

The secondary objectives of this study are: (1) To evaluate the efficacy of the administration of vitamin D3 for enhancing physical performance, decreasing perceived fatigue and achieving serum levels of 25(OH)D above 30 ng/mL; (2) To evaluate the effect on tumour biomarkers; (3) To explore the relationship between vitamin D treatment compliance and 25(OH)D levels; (4) To explore the relationship between 25(OH)D levels and renal function; (5) To explore the dose–response relationship in the group of patients with vitamin D3 for the main outcome; (6) and to assess the cost utility of the proposed administration of vitamin D3.

**METHODS AND ANALYSIS**

The tolerable upper intake level (UL=4000 IU/day or 100 µg/day) has already been established by the European Food Safety Authority for the adult population. However, there is a need for a proof of concept trial to be conducted in patients with advanced cancer in palliative care to gain preliminary data on the safety and efficacy of high doses (at UL) of vitamin D. Therefore, a phase II proof of concept study is planned to obtain reliable data to support a phase III confirmatory trial, within a randomised controlled trial with a placebo two-stage adaptive design.

**Trial design**

A randomised triple-blind phase II/III placebo-controlled multicentre trial has been designed. The randomisation will be based on a computer-generated procedure centralised by the pharmacy service of the coordinating hospital in order to ensure the required treatment allocation concealment. Serum levels of vitamin D will be not available to the patients or their physicians to preserve treatment allocation concealment. A randomised triple-blind phase II/III placebo-controlled trial design has been planned. The randomisation will be stratified by primary solid tumour type in a 1:1 ratio. In a proof of concept trial (phase II or stage 1), patients will be assessed after the first 14 days of treatment about self-perceived changes in HRQoL. The study includes a first interim analysis similar to a futility test to discontinue the trial, and reject vitamin D3, if no better outcome is obtained when compared to the placebo group. Otherwise, it will continue to Phase III (stage 2), which is planned to establish the efficacy in improving and
maintaining HRQoL as well as the safety of the treatment with UL of vitamin D over placebo for 28 days (till day 42 from enrolment). This study will assess the efficacy of vitamin D when administered in combination with the usual palliative care and functional rehabilitation.

**Study setting**

Phase II of the study will take place at Hospital Universitari Armanu de Vilanova (Lleida, Spain). For phase III of the study, three additional Spanish hospitals, Duran i Reynolds (Barcelona), La Paz (Madrid) and Virgen de la Macarena (Sevilla), will participate.

**Patients**

Eligible patients will be adults with a locally advanced or metastatic or inoperable solid cancer in palliative care on signed informed consent. Exclusion criteria will be having a Karnofsky <30%, being pregnant or breastfeeding females, undergoing severe liver or renal (glomerular filtration rate <60 ml/min) failure, having a cognitive deterioration (more than 5 mistakes in the Pfeiffer test), suffering from significant pain, dyspnoea, nausea or vomiting (more than 6 out of 10 in the corresponding Numerical Rating Scale 0:10), hypercalcaemia (> 10.5 mg/dL), having received chemotherapy or radiation therapy within the past 3 weeks prior to inclusion, or having the possibility of initiating a new cycle of chemotherapy or radiation therapy within a period of 6 weeks after their inclusion date.

A prescreening day is scheduled for each adult patient with a locally advanced or metastatic or inoperable solid cancer in palliative care who did not present any known reason to be excluded. On that day, a blood test will be ordered (since results should be available on the screening day for the complete assessment of exclusion criteria) and a visit with the physical rehabilitation medical doctor will be scheduled for the same day.

On the screening day, those patients satisfying inclusion and exclusion criteria will be provided with complete information about the study and enrolled into the study pon signed informed consent.

**Intervention**

Vitamin D3 supplements of 4000 IU/day (UL) or placebo will be added to palliative care treatment on day 14 after enrolment and continued up to day 42. Outpatient visits will be scheduled every 14 days. Supportive evidence for the UL established dose is provided by randomised controlled studies in which this quantity or higher was administered to various population groups for up to 12 months without evidence of persistent hypercalcaemia or hypercalciuria.

Palliative care treatment will be standardised among participating physicians to ensure comparable procedures on symptoms control (pain, nausea, vomiting, constipation, diarrhoea, lack of appetite, shortness of breath, cough and dry mouth).

Functional rehabilitation will be coordinated by the rehabilitation doctor at each participating hospital from day 0. On that day, there will be an evaluation of the clinical and functional status (weakness, effort tolerance, mobility, functional performance and independence in activities of daily living), neuro-orthopaedic disorders, orthopaedic aids necessary to improve the functionality and individualised physical therapy to perform. Three additional sessions will be scheduled before day 14 to work in the following basic protocols: Assisted and free active physical therapy; Respiratory physiotherapy; Rehabilitation of trunk balance in sitting and standing; Re-education in walking; Energy saving measures, and teaching family involvement. Any requirement for additional measures of rehabilitation will be specifically noted. Leaflets containing advice and recommended exercises for functional rehabilitation will be provided to all participating patients and their families.

**OUTCOMES**

**Primary outcome**

Change in patient self-reported HRQoL is the primary outcome. It will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL, a questionnaire developed for patients with cancer in palliative care. It includes rates on: pain, physical function, emotional function, fatigue, global health status/quality of life, nausea/vomiting, appetite, dyspnoea, constipation and sleep. Its scale rating global health status/quality of life using a numbered scoring scale from 1 or very poor to 7 or Excellent is the primary outcome. An anchor question approach is included in order to establish ranges of scores reflecting patient self-assessment of changes in perceived HRQoL (as an approach to minimal important difference assessment).

Since patients with advanced cancer in palliative care can undergo rapid health deterioration (within a few days), primary as well as secondary outcomes will be recorded at baseline and on the allocation day (14 days after enrolment) in order to assess intrapatient variability occurring before any intervention. After starting the intervention, primary and secondary outcomes will be collected on days 28 and 42 from enrolment day (after 14 days and 28 days of taking vitamin D or placebo).

**Secondary outcomes**

Change in cancer-related fatigue is the second most important outcome, and will be assessed with the fatigue subscale of the Functional Assessment of Cancer Therapy:Fatigue (FACT-F) questionnaire. FACT-F is a widely used 13-item fatigue subscale where each item is a five-point Likert self-report scale ranging from 0='not at all' to 4='very much so'. The total score varies from 0='worst condition' to 52='best condition'.

Change in functional capacity is another important secondary outcome and will be assessed using the

Barthel Scale, an ordinal scale that measures performance in activities of daily living, as well as the Karnofsky and the Palliative Performance Scale (PPS) scores, which are used to quantify patients' performance status. All of them provide a score from 100 to 0, where 100 indicates no evidence of disease (normal performance) and 0 indicates death.

Other secondary outcomes include changes in serum levels of 25-hydroxyvitamin D, changes in tumour biomarkers, adherence to the randomised intervention (defined by the proportion of compliance with the randomised intervention out of the total 28 days), renal function and cost utility analyses. Utilities will be based on the patient self-reported HRQoL measured by EuroQoL (EQ-5D; 3 L). This questionnaire assesses five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) to define the health state of patients. Each health state will be translated in the corresponding valuation by applying the Spanish general population utility weights, resulting in valuations from 1 (optimal health) through 0 (as bad as death) to negative values (worse than death). Direct costs will be collected in both groups.

Sample size
The research team considers that a 15% difference is clinically relevant and that differences below 15% will not suffice to demonstrate the clinical significance of the effect of supplementation with vitamin D on quality of life. Therefore, this study is designed to detect differences of 15% or more in the proportion of patients with improved HRQoL between the groups. Error probabilities of α and β to 0.05 and 0.2, respectively, for a unilateral contrast with a 1:1 allocation are fixed for sample size calculations.

The phase II sample size is designed to control early stopping probability based on the exact binomial distribution (Simon, 1989) on optimal two-stage designs and fixed to at least 28 patients per group (optimal design for the first stage). The trial will be stopped if the number of patients that improve is not higher in the intervention group than in the control group.

The total sample size for this study (adding phases II and III) is computed as the minimum number of patients per group to detect differences from 15%, even in the case of maximal requirements that would be having proportions of improvement in HRQoL close to 50%. Therefore, with proportions of improvement in HRQoL of 42.5% for the placebo group and 57.5% for the vitamin D group, and using the same error probabilities in a unilateral contrast, a minimum of 137 patients per group (a total of 274 patients enrolled) are estimated as the minimum sample size required by applying the arctan approximation. Since twice this improvement could be observed in the vitamin D group, an interim analysis is scheduled at the end of treatment for the first 43 patients per group (phase II patients included) in order to minimise the number of patients in the placebo group. If the difference in the proportion of patients with minimally improved HRQoL is twice the expected 15% in favour of vitamin D3, the trial will be stopped for ethical reasons for the benefit of the patients in the placebo group. In other words, the second interim analysis is planned with a stopping rule so that if the improvement difference is 30% or greater, all the participants will benefit. Figure 1 summarises this study design.

Assignment of interventions
The randomisation process will be centralised at the Pharmacy Service of the Hospital Universitari Arnau de Vinalova. The Pharmacy Service will be the responsible for randomising and blindly assigning vitamin D3 or placebo to each patient, stratified by the primary tumour and blocking it to ensure the same number of patients in each intervention. Drug or placebo formulation, labelling and allocation will be performed by the pharmacist, who will create an identifier for each patient, independently from the order of entry into the study. The matching of each patient identifier with its allocated intervention will be saved in an independent database for the exclusive use of the pharmacist or the External Safety Monitoring Committee until the end of the study.

Data collection and management
Figure 2 summarises the data collection and management description that is detailed below.

Data collected exclusively at baseline (day 0)
The inclusion and exclusion criteria checklist and baseline information will be also collected including sociodemographical data (age, sex, education), anthropometric data (height), clinical data (primary tumour, stage and treatment), as well as treatments that may interact with vitamin D (antiepileptics, antihypercholesterolaemic, certain diet drugs and corticosteroids).

Data collected at all visits (days 0, 14, 28 and 42)
Collection will include: anthropometric data (weight, body mass index, triceps skinfold); palliative care treatments (cachexia, pain,...); functional capacity (Barthel, Karnofsky, PPS); cancer-related fatigue (FACT-F...
subscale); and quality of life (EORTC QLQ C15 PAL and EQ-5D). Biochemical data will be separated into one part available during the study for the patient and the physician (PCR, total protein, serum albumin, triglycerides and cholesterol (total, low-density lipoprotein, high-density lipoprotein)) and another available during the study only for the external Data Monitoring Committee (25-hydroxyvitamin D, serum calcium and urinary calcium).

Data collected in the postallocation visits (days 28 and 42)
Patient assessment of change from the start of treatment will be collected in response to the question: Please indicate whether there has been any change in your health related quality of life from the start of treatment by choosing one of the following options: −3, very much worse; −2, much worse; −1, slightly worse; 0, no change; 1, a little better; 2, much better; 3, very much better. An at least minimal improvement is defined for patients with an answer from 1 to 3 to this question.

Reported compliance per day starting on day 15 will be also collected.

Most people are not expected to suffer from any side effect, unless they take more than the prescribed amount of vitamin D. Hypercalcaemia and patient assessment of weakness, fatigue, drowsiness, headache, loss of appetite, dry mouth, metallic taste, nausea or vomiting are the adverse events listed in the bibliography. Adverse events will be collected using an ordinal scale of four categories for each one: 'No (0 points)', 'Mild (1 points)', 'Moderate (2 points)' and ‘Severe (3 points)’. All adverse events happening postintervention (from 15th to 48th day) will be recorded throughout the study, registering: the adverse event name, starting and ending dates, frequency, severity, intensity, relationship to study drug, action taken and resolution.

Any suspected unexpected serious adverse reaction (SUSAR) will be reported to the Spanish Agency (AEMPS). An SUSAR is defined as any adverse reaction to vitamin D which shows a reasonably and unexpected causal relationship, whose nature, severity or outcome is not consistent with the summary of the characteristics of the technical data and that produces death, endangers the patient’s life immediately, produces a persistent or significant disability, requires or prolongs hospitalisation, or becomes a significant danger that is comparable to the above criteria.

Statistical analysis
For the first interim analysis, only the number of patients with at least minimally improved HRQoL will be compared, with no statistical test to base the decision to stop. For the second interim analysis, a difference between response rates of 30% or higher will be used to make the decision to stop. At the end of the study, a descriptive univariate analysis of each group will be performed, followed by a comparison between groups to check if randomisation produced comparable groups in each potential confounder. Bivariate analyses will use the Mann-Whitney or $\chi^2$ test for quantitative or qualitative variables, respectively. In case of differences, analysis of minimally improved HRQoL by logistic regression will be performed adjusting for them. For differences between groups in longitudinal measurements (such as chemistries), linear and non-linear mixed-effect models will be used. Additionally, for the intervention group (patients treated with vitamin D), longitudinal measures of serum vitamin D and renal function will be related by fitting mixed effects linear models. Main outcomes will be analysed by intention to treat. A longitudinal analysis of treatment compliance (cumulative dose in both periods of 14 days) will be performed in relation to serum vitamin D levels as well as an analysis per protocol to look at dose–response effects. Finally, a cost utility analysis of the intervention with cholecalciferol will be performed. For each patient, quality-adjusted life years

Figure 2  VIDAFACT participant timeline.
will be calculated as the area under the EQ-5D utility curve. Since patients with missing values from questionnaires are likely to be worse than those with the available measurements, the missing outcomes will be imputed using non-linear regression models. A p<0.05 will be established as statistically significant. R software will be used.42

ETHICS AND DISSEMINATION

Any amendment will be immediately communicated to both agencies. All participants will provide signed informed consent and their confidentiality will be guaranteed by encoding all personal information. Insurance will cover any unexpected damage attributable to participation in the study.

Ethical implications

An external Safety Monitoring Committee has been created, comprised of one physician external to the study from each of the participating hospitals. They will be responsible for monitoring participants’ calcium and vitamin D levels during the study in order to ensure the patients’ safety and allocation concealment. The research team has no economical interest in favour of or against vitamin D supplementation. Its only interest is to provide evidence as to whether vitamin D supplementation is beneficial or not for patients with advanced cancer in palliative care. Criteria to stop after any of the two planned interim analyses are clearly established in the study protocol. After each interim analysis, blindly performed by the statistician of the research team, the pharmacy service will assess the results of interim analyses in relation to the stopping rules established in the protocol and with their exclusive knowledge of the intervention groups. They will be responsible for communicating the end or the continuation of the study based on the criteria established in the study protocol to the research team. The two interim analyses and the phase II/III study design are part of this protocol to minimise the use of time and patients required to demonstrate whether, as hypothesised, there is a clinically significant benefit from the use of vitamin D in patients with advanced cancer in palliative care. The size of the group randomly assigned to placebo is minimised during the study and, if the effect of vitamin D interventions become conclusive, this group will also be supplemented with vitamin D.

Dissemination policy

Given this project’s scientific and social interest, its results will be locally and internationally disseminated in congresses, scientific papers and the media.

DISCUSSION

The potentially high scientific and social interests of this project, fully based on the premise that ‘When no curable treatment is possible, palliative care should be directed towards minimizing symptoms, relieving suffering and bringing patient to the best possible health related quality of life’, can be summarised as follows: Scientifically:

1. The results of this safe, cost-effective intervention with vitamin D supplementation in patients in palliative care research would be, to the best of our knowledge, the first attempt to conclusively address whether the quality of life for these patients could also improve from the prosurvival properties of a normal vitamin D status, as reported not only in healthy individuals but also in those with diabetes, hypertension, cardiovascular disease, autoimmune disorders, tuberculosis, kidney disease and cancer.

2. This work could provide evidence-based recommendations for the efficacy of vitamin D supplementation to patients in palliative care in improving their quality of life. Such a finding could be immediately incorporated into clinical practice due to its low cost and lack of toxicity. Furthermore, if confirmed, these findings should provide a solid basis for the design of prospective, well-powered clinical trials directed at customising vitamin D supplementation regimens in order to expedite the correction of vitamin D deficiency in treatment-resistant patients and, more importantly, ensure the fast improvement of their quality of life.

3. It could help initiate new lines of research on the pathogenesis of cancer-related fatigue to prevent its onset at early stages and attenuate its progression in cancer.

4. It could bring basic and clinical research together in the arena of advanced cancer.

5. The most optimistic outcome would be to change the ‘current paradigm’ for patients in palliative care from a state of ‘no curable treatment possible’ to a vitamin D healing transition making the patient eligible for a new customised cancer therapy with vitamin D as a coadjuvant therapy.

Socially:

1. For the individual: The possibility of giving a patient in palliative care a safe, non-costly, and evidence-based effective option to maintain their quality of life, and the hope that they could eventually become eligible to restart cancer therapy for a cure is invaluable.

2. For the community: This is research with a potentially high clinical relevance, completely independent from the interests of the pharmaceutical industry, whose results could benefit patients in palliative care even in underdeveloped countries with the poorest of healthcare systems.

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REFERENCES

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