

Biostatistics Collaboration of Australia

University of Sydney

Work Placement Project Portfolio

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Sydney, November 2008

Does a mild anti-depressant improve quality of life in patients with advanced cancer?

The ZEST Trial

A double-blind, placebo-controlled trial of
**Zoloft's Effects on Symptoms and survival Time in
Advanced Cancer**

NHMRC Clinical Trials Centre, University of Sydney

NSW Cooperative Oncology Group

Preface

Background

Diagnosis and proper treatment for patients with depression can improve their quality of life. The physical symptoms of depression include: change in appetite/weight, sleep disturbance, fatigue, loss of energy, diminished ability to think or concentrate etc. Depression is a common scenario in cancer patients especially in advanced stage. It impacts on mental health and can influence the medical course of the patient. Effects on mental health include: undermining the will to live, increasing desire to hasten death etc. Depression can accelerate the progression of cancer disease and consequently influence a patient's survival.

A number of small trials have been conducted which demonstrated that conventional antidepressants may improve fatigue and QoL in people with cancer and major depression. A large trial is needed to assess a simple, safe and effective antidepressant in people with advanced cancer who feel anxiety, depressed or tired but do not have major depression. Hence the ZEST trial was undertaken.

The ZEST trial is a randomized, double-blinded, multi-center trial of sertraline versus placebo using appropriate patient rated outcome measures where the primary objective is to determine the effect of a modern antidepressant (sertraline) on feelings of depression, anxiety, fatigue and lack of energy. The secondary objective is to determine the effect on overall survival.

In February 2006 in response to a recommendation from the trial's Independent Safety Data Monitoring Committee the trial was suspended.

Reflections on learning

Through this project I have learnt how to implement statistical methods in real life analysis. We have covered many statistical methods in the BCA courses but in this project I have learnt how to apply these methods in practical problems. This project gave me a good opportunity to obtain experience of data analysis using statistical software STATA. Now I have a better understanding of randomized controlled trials and how to analyze data from a randomized trial. After completion of this project, I have a strong belief that BCA courses are designed to solve practical problems and now I think I can analyze all sorts of data in future.

Student's role

As a student my role was to prepare and manipulate the raw data for analysis, and subsequently apply appropriate statistical methods to analyze the data according to the study objectives. Survival analysis methods such as the log-rank test and cox proportional hazards models were used to analyze time to event outcomes. Generalized Estimating Equations (GEE) were used for the primary QoL analysis. This method adjusts for the intra-subject correlation owing to subjects having repeated QoL measurements. I had to carry out related data management tasks defined by the project supervisor. The analysis was carried out using STATA and SAS software. I would make proposals to my supervisor concerning which statistical methods should be applied to address the study objectives. I also prepared the layout of the tables and figures. My supervisor would then provide feedback which I acted upon. Several iterations of the analysis and text for the trial results report were conducted until the work was finalized. The final analysis was completed within 3 months of the trial close-out date according to the study protocol.

Before analysis could commence the data needed to be cleaned. Through this task I have gained insight into the types of data errors that occur and appreciate the importance of running data checks and queries prior to analysis. The statistical analysis included: data manipulation, calculating scores, running appropriate statistical procedures, interpreting

results and transcribing results into a table for presentation. To do this I had to apply my knowledge and understanding of the theory and methods learnt during the BCA course.

Communication skills

During this project I had regular meetings with the project supervisor to discuss associated problems and issues. All through this project I had one regular weekly face to face meeting and other communications were through e-mail and telephone when necessary.

Team work

I worked on this project under direct supervision of the project supervisor. We liaised with the trial investigators to discuss results and additional analyses when necessary. There were other people involved in this project but no direct involvement with them was necessary.

Ethical considerations

There were ethical considerations for this project. The data were collected and finalized before the analysis was conducted. Patients were de-identified using ID's and no other personal information was present. The ZEST trial obtained ethics approval before randomization of patients onto the trial began. All sorts of actions were taken to ensure privacy and confidentiality of data. The trial protocol was approved by human-research ethics committees at all participating institutions. The data will be stored on the NHMRC CTC network at least for 10 years.

Workplace Project Portfolio

Project title

Does a mild anti-depressant improve quality of life in patients with advanced cancer?

Location and dates

NHMRC Clinical Trials Centre, University of Sydney.
August 2008-November 2008.

Aim

To determine if a modern antidepressant (sertraline) improves subjective well-being and survival in a broad cross-section of people with advanced cancer who feel depressed, anxious, tired or lack energy, but do not have major depression.

Objectives

To determine the effects of a modern antidepressant (sertraline) on

1. Feelings of depression, anxiety, fatigue and lack of energy (primary objective)
2. Overall survival (secondary objective)
3. Adverse events (tertiary objective)
4. Compliance (tertiary objective)

Study design

Multicentre, double-blind, placebo-controlled trial with central randomization, stratified to balance for institution, gender, future cytotoxic treatment anticipated (yes or no) and performance status (ECOG 0-1 or 2).

Population

Simple eligibility criteria based on the uncertainty principle: people with advanced cancer in whom there is doubt about the benefits of treatment with antidepressants.

Study treatments

Sertraline 50mg, one tablet once daily by mouth with or without food

or

Identical placebo, one tablet once daily by mouth with or without food.

Sertraline (Zoloft) is a selective inhibitor of serotonin reuptake (SSRI). It has little or no effect on reuptake of noradrenaline or dopamine. It has little or no effect on receptors for serotonin, noradrenaline, dopamine, acetyl choline, Gamma amino butyric acid (GABA), Histamine, or benzodiazepines. It is of proven benefit in major depression, obsessive compulsive disorder, panic disorder.

Acknowledgements

I would like to thank Prof. Val Gebski for allowing me access to the data and giving me the opportunity to analyze the data, and Ms. Rachel O’Connell for her assistance and guidance regarding analyzing the data, choosing appropriate statistical methods and correctly interpreting the results.

Declaration

Declaration by Student

I declare that this project is evidence of my own work, with direction and assistance provided by my project supervisor, Rachel O’Connell. This work has not been previously submitted for academic credit.

.....
Syed Azim

.....
Date

Comments and Declaration by Project Supervisor

The declared contributions by this student are true and correct. To my knowledge, the involvement and effort of this student for this project is satisfactory for the requirements of a BCA Workplace Project.

.....
Rachel O’Connell

.....
Date

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Project Report

Introduction

Cancer is a common disease in Australia. About 1 in 4 Australians develop advanced cancer and over 33,000 Australians die from advanced cancer each year.¹ About 1 in 5 people with cancer have major depression during their illness;²⁻⁴ symptoms of depression in the absence of major depression are even more common.⁵⁻⁷ In a sample of 1109 community oncology out-patients, 35% had clinically significant depression based on the Zung Self-Rating Depression Scale; the incidence of depression increases with advanced stage, physical debilitation and pain.⁴ Fatigue is highly prevalent among people with advanced cancer. In a sample of over 1000 patients with advanced cancer assessed with the Functional Assessment of Cancer Therapy – General (FACT -G), fatigue was reported by about 75% of patients; sadness and anxiety were each reported by about 60% of patients.⁸ Self-ratings of depression, anxiety and fatigue are closely correlated with one another and with global ratings of quality of life in people with advanced cancer.⁷ Their causes are multi-factorial and difficult to separate.^{9,10}

Depressed mood, fatigue, and global quality of life are also highly significant predictors of survival in advanced cancer.^{6,7,11} The simple explanation for this association with survival duration is that people closer to death feel worse. However, two small randomized trials have shown substantial survival benefits with interventions aimed at improving psychological well-being.¹²⁻¹⁴ These findings suggest that a much more interesting alternative is worth testing: that improving psychological well-being prolongs survival in advanced cancer. Large randomized trials testing this hypothesis are ongoing in Canada and Australia.¹⁵

Antidepressant drugs might improve psychological well-being in people with advanced cancer. Systematic reviews of randomized trials demonstrate the effectiveness, tolerability and modest side effects of conventional antidepressants (e.g. sertraline) in major depression with coexisting physical illness (18 trials, 838 patients).¹⁶ Four small

randomized trials suggest that conventional antidepressants are effective and well-tolerated in people with cancer and major depression, and that they may also improve fatigue and overall quality of life.¹⁷⁻²⁰

Antidepressants, especially selective serotonin reuptake inhibitors – are prescribed widely, not only for their standard indicators, but also for a wide range of subthreshold anxiety and depression disorders, especially in patients with comorbidity.²¹ Antidepressants have been used widely in patients with cancer, and those with other chronic diseases, as management for chronic pain, insomnia, chronic fatigue, and anxiety or distress associated with physical illness.

We aimed to find out whether an established antidepressant (sertraline) improves well-being in patients with advanced cancer who feel depressed, anxious, tired or lack of energy, but do not have major depression. We postulated that sertraline might improve these features of health-related quality of life and increase overall survival by helping patients to cope better with their illness and treatment.

Objective

The objective of this study was to determine the effects of a modern antidepressant (sertraline) on feelings of depression, anxiety, fatigue and lack of energy, overall survival, adverse events, compliance and reasons for discontinuation.

Hypotheses

That a modern antidepressant (sertraline) will:

- 1) Improve depression, anxiety, fatigue, lack of energy and other aspects of health-related quality of life and
- 2) Improve overall survival by helping people to deal better with their illness and treatment.

Methods

Description of trial design

The ZEST trial was a multicentre, double-blind, placebo-controlled, centrally randomised trial that was stratified for institution, sex, anticipated future cytotoxic treatment (ie, yes vs no) and Eastern Cooperative Oncology Group performance status (ECOG PS 0-1 vs 2) by use of a computerised minimisation algorithm. Randomisation was done over the telephone by the study coordinator at the NHMRC Clinical Trials Centre, University of Sydney, NSW, Australia, after confirmation of each patient's eligibility.

The trial protocol was approved by human-research ethics committees at all participating institutions.

Participants

Eligible patients were those with advanced cancer, in whom there was doubt about the benefits of treatment with antidepressants. Inclusion criteria included: advanced cancer defined by the presence of metastatic disease and treatment with palliative intent; a self rating baseline score $\geq 4/10$ for depression, anxiety, fatigue or lack of energy (here 4 means moderate); ECOG performance status 0-2; life expectancy of >3 months; serum creatinine <200 micromol/L and bilirubin <30 micromol/L within 28 days of randomization; able to complete baseline quality of life instruments; availability and willingness for follow-up; written informed consent. Women of childbearing potential must need to take adequate contraceptive precautions.

Exclusion criteria included: major depression; delirium as detected by the Confusion Assessment Method; coexisting conditions contraindicating treatment with serotonin reuptake inhibitors; history of hypersensitivity to sertraline; diagnosis of carcinoid tumour; past history of schizophrenia or bipolar affective disorder; treatment with antidepressants (including St John's Wort) or procarbazine within the last 4 weeks; pregnant or lactating women; treatment with tramadol in the last 7 days. (ZEST

participants should not use Tramadol because of the possibility of an interaction causing the serotonin syndrome).

Recruited oncologists were instructed that any potential participants whom they thought might have major depression should be referred to the psychiatrist co-investigator at their institution. If the psychiatrist thought that there was a definite indication for antidepressants, the patient was treated off-study and not recruited to the trial.

Study treatment

Study treatment was with either sertraline 50mg, one tablet daily by mouth or with a placebo of identical appearance (both provided by Pfizer). Study treatment was to continue indefinitely in the absence of prohibitive toxicity. The decision to stop study treatment because of adverse events, or to recommence it if they resolved, was at the discretion of the patient and physician. Dose adjustments were not recommended. Discontinuation was to be done gradually if possible, by reducing the daily dose to 25mg (half a tablet) for 1 week before stopping completely.

Concomitant anticancer and supportive treatments (including psychological, psychiatric, social and other supports) were used according to standard local practice. Participants who developed symptoms of major depression were to be referred to the psychiatrist co-investigator at that centre. If the psychiatrist believed that there was a definite indication for antidepressants, then the ZEST Study Drug was discontinued and patients were started on antidepressants under the psychiatrist's supervision.

Study assessment

Symptoms, well-being and quality of life were self-rated by patients at weeks 0, 4, and 8 with a booklet including necessary instruments. The booklet was completed by the study participants in the clinic while they were waiting to see their oncologists. Study nurses checked the booklets and asked participants to complete missing responses. Missing

responses were therefore infrequent. The forms were masked from identification and patients' study numbers were used to link the forms to patients.

The Centre for Epidemiologic Studies Depression Scale (CES-D, 20 items) is a validated measure for identifying depression in the general population. The Hospital Anxiety and Depression Scale (HADS, 14 items) is a validated measure of anxiety and depression in the medically ill people.²² The Functional Assessment of Cancer Therapy General and Fatigue scales are validated measures of the broad symptomatology (FACT-G, 27 items) and fatigue (FACT-F, 13 items) associated with cancer. The Fatigue scale was used for this study. The Patient Disease and Treatment Assessment Form (Patient DATA Form, 24 items) is a single-page measure rating 17 symptoms and 7 aspects of well-being on numeric ratings scales from 0 to 10.

For CES-D we analyzed all 20 questions on the form to derive an overall depression scale. For HADS, we analyzed all 14 questions; these questions were divided into two groups to derive overall scores for anxiety and depression. From Patient DATA form, 3 questions were analyzed for fatigue, anxiety and depression. For FACT-F, all 13 questions were analyzed to derive an overall score for fatigue.

When calculating overall scores it was necessary to reverse the scores for some items so that the direction of the scales was consistent across all items.

Clinicians assessed performance using the ECOG and Karnofsky scales.²² ECOG and Karnofsky scales were used to obtain a rating of the patient's health performance (i.e., level of functioning and disability) at baseline.

Planned sample size

The intended sample size was 440 patients, recruited over 3 years and followed for 1 additional year. This was calculated based on a minimum clinically important difference of 10 points and a standard deviation of 25 on a 100-point scale (for depression, fatigue, lack of energy)²⁴⁻²⁶ with a two-sided alpha (p-value) of 0.01 (adjusted down for multiple comparisons). Two hundred patients per arm would give over 90% power to detect the

superiority of antidepressants over placebo in improving QoL (depression, anxiety, fatigue) and would detect a 50% improvement in median survival time (eg 8 to 12 months).

Planned interim analyses

Interim analyses was planned to be performed on data collected 12 weeks after randomization of the 150th and 300th patients focusing on safety (frequency and severity of adverse events), feasibility (completion of 8 weeks of therapy, follow-up at 8 weeks) and survival. The results were to be reported to an independent Safety and Data Monitoring Committee (DSMC). The DSMC is guided by conservative notional significance levels of $2p = 0.003$. Based on these results, the DSMC would advise the Trial Management Committee whether to stop, expand or modify the trial.

Interim analysis was conducted by another statistician and final analysis was conducted by me.

Statistical analyses

All efficacy analyses were done by intention to treat and included all patients, regardless of whether they were taking their allocated treatment. Toxicity analyses included all patients who had taken study treatment within the past 30 days. Reported p-values are 2-tailed, and should be interpreted conservatively because they have not been adjusted for multiple comparisons.

Quality of life:

The primary measures for each quality of life outcome were the: CES-D for depression, HADS-A for anxiety and FACT-F for fatigue. Alternate measures of these outcomes, for example the HADS-D for depression and items from the Pt DATA Form, were used for corroboration. The primary analysis was a comparison of the treatment groups based on scores at 4 and 8 weeks using generalized estimating equation (GEE) regression models with treatment group and baseline scores as covariates. An exchangeable correlation structure was used for the GEE model. The randomization procedure was stratified to balance for center, grade, future cytotoxic treatment and ECOG performance status.

Hence it is not necessary to adjust for these factors in the multivariate analysis, as they should have been and were balanced between the two treatment arms. For the repeated measures analysis time was not included as a covariate which effectively meant that the treatment effect estimate and least square adjusted mean scores for each treatment group were calculated based on the average of the 4 and 8 week scores for each subject. The advantage of this is that using an average of 2 repeated measurements is more reliable and reduces measurement error compared to using a single measurement. Since time was not a covariate we did not need to include any random effects in the model (i.e., modeling time as a random effect allows the effect of time on QoL to be patient-specific), hence a GEE model was sufficient. A suitably specified random effects mixed model would give similar results and conclusions. For this analysis scores for all aspects of health-related QoL were linearly transformed to a scale from 0 to 100 where 0 is the best and 100 worst. Patients required a score at either 4 or 8 weeks or both to be included in this modeling analysis. Patients that only had 1 of the 4 and 8 week time points for the QoL scores are still included in the GEE analysis. These patients contribute to the estimation of parameter estimates but not the correlation matrix which contributes to the estimation of standard errors for parameter estimates.

Secondary measures of effect included the proportions of people having an improvement greater than 20% of the response range (eg 2 points on a scale from 0 to 10) from baseline to weeks 4 and 8. Fisher's exact test was used to compare major improvement between treatment groups due to low cell counts (<5). The Fisher's exact test is conservative since the row and column marginal totals are allowed to vary. An additional sensitivity analysis was later conducted using the conditional binomial exact test which fixes the treatment column totals; conclusions were unchanged.

When calculating QoL scores patients were required to complete at least 66% of the items which constituted that dimension; otherwise the score was set to missing.

Safety and adverse events:

Safety and adverse events were categorized and graded according to version 2 of the US National Cancer Institute common toxicity criteria.

For each patient the maximum severity (grading from 0 to 4) experienced for each of the 11 adverse events was determined. The proportions of patients with 0, 1, 2, 3 and 4 as their worst grade for each adverse event were tabulated by treatment group. Patients not experiencing a specific adverse event were graded as zero for that event. Patients with no data for all the adverse events (i.e., missing) were excluded. Due to the nature of the follow-up visits and to ensure that no adverse events that could have been attributed to treatment are missed, the events reported during assessments performed up to the assessment following the treatment termination date plus 30 days were included. Adverse events occurring after this time are not likely to be related to treatment.

For the laboratory analysis patient's biomarkers (WCC, Lymphocytes, Hemoglobin etc) were also graded using cutoffs from version 2 of the US National Cancer Institute common toxicity criteria. Analysis of patient's blood levels will determine whether there is an excess of toxicity in the active treatment arm. Only biomarker data collected during the first year of follow-up was used for this analysis. Laboratory tests performed up to the treatment termination date plus 30 days and additionally results from the first laboratory test done after this date were included. Toxicities occurring after this time are not likely to be related to the treatment. Cutoffs indicate which levels are within normal range, and above or below upper/lower limits of normal ranges. An extreme biomarker reading (e.g. $\geq 5 \times \text{ULN}$, Upper Limit Normal) will have a severe grade (e.g. grade IV). Laboratory readings within normal limits receive a grade of zero. Values outside the normal limits receive a grade ranging from 1 to 4 depending on how abnormal the reading is. For example for Hemoglobin the extreme grade (i.e., grade 4) is $<6.5 \text{ g/dL}$, grade 3 is $6.5 - <8.0 \text{ g/dL}$, grade 2 is $8.0 - <10.0 \text{ g/dL}$, grade 1 is $<\text{Lower Limit Normal (LLN)} - 10.0 \text{ g/dL}$ and grade 0 if it is $\geq \text{LLN}$.

The Mann-Whitney U test [also called the Mann-Whitney-Wilcoxon rank-sum test] was used to test for differences in worst grades obtained between treatment arms for the adverse events and laboratory analysis. This test was used because it is a non-parametric test for assessing whether two treatment groups come from the same distribution. Due to the skewed distribution of the adverse event and toxicity grades this test was appropriate for this analysis. As it is a non- parametric test, it does not require normality or equality

of variance. This test uses the ranks of the data rather than their raw values to calculate the p-value.

Overall survival and treatment failure:

The secondary endpoint overall survival was calculated from the date of randomization to date of death for any cause.

The primary analysis for effects on survival was an unadjusted log-rank test. The log-rank test is used to compare the survival distributions of groups and is widely used in clinical trials to establish the efficiency of a new treatment compared to the current standard treatment.²³ The log-rank test was used because an unadjusted analysis was required for the primary analysis and the log-rank method provides the most powerful test. The log-rank method takes into consideration the area between the curves on a Kaplan-Meier plot and provides the most pure measure of statistical significance. In addition the log-rank test does not make any assumptions unlike the proportional hazards cox model which constrains the relative effect over time between groups to be constant. Multivariable Cox's proportional-hazards models were used for secondary analyses accounting for other baseline factors. The multivariable analysis was conducted to confirm the results of the unadjusted log-rank test. The adjusted analysis controls for any minor chance imbalance in baseline characteristics between the treatment arms. A series of univariate cox models were fitted as a preliminary step. Baseline variables with p-value <0.05 in univariate analysis were considered for inclusion in the multivariable analysis. The multivariable analysis was conducted by running a backward elimination procedure, and selecting from the pool of variables with p-value <0.05 in univariate analysis. Treatment was forced into the model and only significant (p<0.05) baseline covariates were retained. This determined the final model.

A caveat of this approach for the multivariable analysis is that only variables that were significant in univariate analysis were considered for inclusion in the backward selection procedure. It is possible that variables were excluded which become significant after adjusting for other variables. The variables which were not considered were balanced between treatment arms anyway and were highly non-significant in univariate analysis.

So, we doubt that the conclusion would have changed if all variables were entered into the model building procedure.

For univariate Cox models most of the covariates had no missing values. For body weight there were 5 missing values and all QoL scores had 3 missing values except FACT-F which had only 2 missing values. For all the covariates selected for inclusion in the final model, there were no missing values.

Treatment failure was defined as time to permanently discontinuing study medications. Temporary stopping was allowed and was not counted as a failure. To compare treatment failure between the two treatment arms the log-rank test was used.

A Cox model was also used to obtain a hazard ratio and 95% CI to obtain a measure of effect for the risk of terminating treatment for sertraline patients relative to placebo patients.

Kaplan-Meier curves were constructed for all time-to-event analyses. For all Cox models the proportional – hazards assumption was checked using plots of schoenfeld residuals. This involves plotting residuals for each covariate versus follow-up time. Schoenfeld residuals differ from the usual way residuals are regarded for a model (one residual for each case) in that there is a residual for each explanatory variable included in the model. Plots of these residuals versus time can reveal departures from the proportionality assumption. These residuals are also used in the Harrell-Lee test of proportional hazards which uses the correlation coefficient between the residuals and rank of the times.

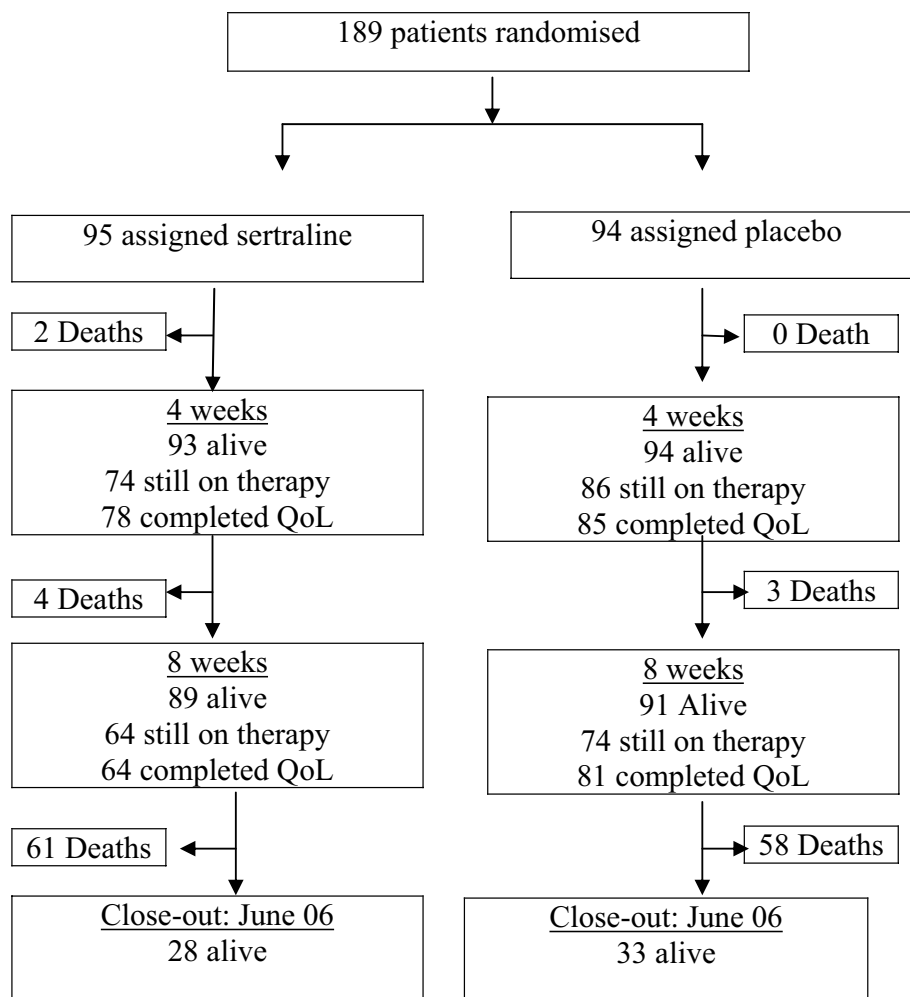
Compliance

Compliance with study treatment was monitored by counting tablets.

Results

Twelve weeks after the 150th patient was recruited interim analysis was conducted on the first 150 patients as planned. This revealed a trend towards shorter survival in the sertraline group than in the placebo group ($p = 0.04$, median follow-up of 15 months) and in response to a recommendation from the trial independent DSMC, recruitment was suspended. The results of this report are based on the 189 patients, recruited from July, 2001, to February, 2006, which comprise the final trial cohort. Figure 1 shows the trial profile.

Figure 1: Zest Trial Profile



Patients still on study treatment were contacted, informed of the results, and given the option of stopping or continuing study treatment whilst definitive analyses were done including all 189 patients and longer follow-up and data for health related QoL. Blinding was maintained.

The following results (Tables 1 & 2) are based on the 189 patients.

Table 1: Baseline characteristics by treatment group

	Sertraline (n = 95)	Placebo (n = 94)	Total (n = 189)
Age			
<50	12 (12%)	3 (3%)	15 (8%)
50-59	18 (19%)	24 (26%)	42 (22%)
60-69	34 (36%)	33 (35%)	67 (36%)
70+	31 (33%)	34 (36%)	65 (34%)
Gender			
Male	55 (58%)	56 (60%)	111 (59%)
Female	40 (42%)	38 (40%)	78 (41%)
ECOG			
0	13 (14%)	8 (9%)	21 (11%)
1	60 (63%)	67 (71%)	127 (67%)
2	22 (23%)	19 (20%)	41 (22%)
KPS			
50	1 (1%)	1 (1%)	2 (1%)
60	5 (5%)	3 (3%)	8 (4%)
70	16 (17%)	20 (21%)	36 (19%)
80	48 (51%)	41 (44%)	89 (47%)
90+	25 (26%)	29 (31%)	54 (29%)
Cancer Stage			
I	10 (11%)	6 (7%)	16 (9%)
II	18 (20%)	20 (22%)	38 (21%)
III	23 (26%)	22 (25%)	45 (25%)
IV	38 (43%)	41 (46%)	79 (45%)

	Sertraline (n = 95)	Placebo (n = 94)	Total (n = 189)
Primary Cancer Site :			
Lung	19 (20%)	10 (11%)	29 (15%)
Breast	17 (18%)	15 (16%)	32 (17%)
Prostate	10 (11%)	16 (17%)	26 (14%)
Colorectal	8 (8%)	21 (22%)	29 (15%)
Other	41 (43%)	32 (34%)	73 (39%)
Involved Sites :			
Loco-regional	53 (56%)	48 (51%)	101 (53%)
Bone Metastasis	36 (38%)	32 (34%)	68 (36%)
Lung/Pleural Metastasis	34 (36%)	29 (31%)	63 (33%)
Brain Metastasis	4 (4%)	2 (2%)	6 (3%)
Other Distant Metastasis	17 (18%)	22 (24%)	39 (21%)
Previous Anticancer Therapy :			
Previous surgery	55 (58%)	59 (63%)	114 (60%)
Previous radiation therapy	52 (55%)	40 (43%)	92 (49%)
Previous/Current endocrine therapy	32 (34%)	30 (32%)	62 (33%)
Previous/Current chemotherapy	78 (83%)	78 (83%)	156 (83%)
Current chemotherapy	54 (57%)	57 (61%)	111 (59%)
Previous interferon or interleukin	0 (0%)	0 (0%)	0 (0%)
Current Opioid use	31(33%)	18 (19%)	49 (26%)
Patient Symptoms :			
Shortness of Breath	39 (41%)	35 (37%)	74 (39%)
Eating	15 (16%)	13 (14%)	28 (15%)
Appetite	38 (40%)	28 (30%)	66 (35%)
Trouble swallow	7 (7%)	8 (8%)	15 (8%)
Dry Mouth	25 (26%)	10 (11%)	35 (19%)
Weight Loss	29 (31%)	21 (22%)	50 (26%)
Fatigue	85 (89%)	87 (92%)	172 (91%)
Life Expectancy (months) :			
< 6	6 (11%)	3 (5%)	9 (8%)
6-9	21 (37)	30 (52%)	51 (45%)
10-15	18 (32%)	13 (22%)	31 (27%)
16-24	10 (18%)	10 (17%)	20 (17%)
24+	1 (2%)	2 (4%)	3 (3%)

Table 2: Baseline blood levels and time to advanced disease (median [IQR])

	Sertraline (n = 95)	Placebo (n = 94)	Total (n = 189)
Blood Test :			
WCC (x10 ⁹ /L)	6.4 (4.3- 7.8)	6.55 (5.1-8.1)	6.4 (4.8-8)
Lymphocytes (x10 ⁹ /L)	1.4 (1-2)	1.4 (1-1.9)	1.4 (1.2)
Hemoglobin (g/dL)	12.3 (10.9-13.4)	12.25 (11.5-13.6)	12.3 (11.2-13.5)
Platelets (x10 ⁹ /L)	232 (182-320)	252 (186-313)	244 (185-319)
Serum albumin (g/L)	37.31 (4.79)	37.85 (4.78)	37.58 (4.78)
Serum sodium (mmol/L)	138 (136-140)	139 (137-141)	139 (137-141)
AST (IU/L)	25 (18-34)	23 (18-31)	25 (18-32)
ALT (IU/L)	22 (17-35)	21 (16-30)	21 (16.5-30.5)
Gammagt (IU/L)	38 (23-93)	46 (24-99)	44 (23-98)
ALP (IU/L)	100 (80-155)	103.5 (81-145)	102 (81-152)
CRP(x10 ⁹ /L)	12 (5-35)	9 (4-23.5)	10 (5-29)
Creatinine (µmol/L)	77 (63-98)	74 (56-91)	75 (60-95)
Time to Advanced Disease (median)	7.8 (0-42.9)	9.4 (0-36.1)	9.0 (0-38.3)

Description of overall population

Tables 1 & 2 show the baseline characteristics of the participants. Most of the participants are male (59%) and aged persons (60+). Seventy eight percent of participants had an ECOG grade of less than or equal to 1 which is good performance status (i.e., able to carry out activities). One hundred and forty three (76%) patients had KPS of 80-90 meaning normal activity with/without effort; some/minor signs or symptoms of disease.

The lowest number of participants belonged to cancer stage 1 (9%) and highest in stage 4 (45%). A large number of patients were currently having chemotherapy (59%). Just over half of the patients had less than 9 months life expectancy (53%).

Differences between treatment groups

The randomization was effective with some minor exceptions. In the sertraline group there are more participants with lung cancer, fewer with colorectal cancer, and more using opioids at baseline than the placebo group.

Description of QoL for total population

Table 3 shows participants' QoL self-ratings at baseline. Forty seven (26%) of 189 patients had scores consistent with clinical depression according to the CES-D. Twenty five (13%) of 189 patients had scores consistent with clinical anxiety according to the HADS-A. Ninety three 93 (50%) of 189 patients had scores consistent with moderate or worse fatigue according to the FACT-F.

Table 3: Baseline ratings of depression, anxiety and fatigue

Aspect, instrument and interpretation	Scores	Sertraline (N = 95) n (%)	Placebo (N = 94) n (%)	All (N = 189) n (%)
Depression				
CES-D				
Unlikely	<15	50(53%)	43(47%)	93(50%)
Possible	15-19	19(20%)	27(29%)	46(25%)
Likely	>19	25(27%)	22(24%)	47(26%)
HADS-D				
Normal	0-7	72(78%)	70(75%)	142(76%)
Subclinical	8-10	12(13%)	17(18%)	29 (16%)
Clinical	>10	9(9%)	6(7%)	15 (8%)
Pt-DATA Form				
None	0	24 (26%)	23(26%)	47(26%)
Mild	1-3	34(36%)	40(44%)	74(40%)
Moderate	4-6	29(31%)	21(23%)	50(27%)
Severe	7-10	7(7%)	6(7%)	13(7%)
Anxiety				
HADS-A				
Normal	0-7	66(70%)	66(72%)	132(71%)
Subclinical	8-10	14(15%)	15(16%)	29(16%)
Clinical	>10	14(15%)	11(12%)	25(13%)
Pt-DATA Form				
None	0	21 (23%)	19 (21%)	40 (22%)
Mild	1-3	31 (34%)	38 (42%)	69(38%)
Moderate	4-6	30 (32%)	25 (28%)	55(30%)
Severe	7-10	10 (11%)	8 (9%)	18(10%)
Fatigue				
FACT-F				
None	0-17	22(23%)	30(33%)	52(28%)
Mild	18-23	23(24%)	19(21%)	42(22%)
Moderate	24-43	45(48%)	41(44%)	86(46%)
Severe	44-52	5(5%)	2(2%)	7(4%)

Aspect, instrument and interpretation	Scores	Sertraline	Placebo	All
		(N = 95) n (%)	(N = 94) n (%)	(N = 189) n (%)
Pt-DATA Form				
None	0	0(0%)	1(1%)	1(1%)
Mild	1-3	9(10%)	8 (9%)	17(9%)
Moderate	4-6	56(59%)	53(59%)	109(59%)
Severe	7-10	29(31%)	28 (31%)	57(31%)

Description of effects of treatment on QoL:

In both treatment groups patients completed QoL at baseline. In the sertraline group at 4 weeks 78 completed QoL, 70 of which were still taking study medication. At 8 weeks 64 completed QoL questionnaires, 59 of which were still on treatment.

In the placebo group at 4 weeks 84 patients completed QoL questionnaires of which 82 were still on treatment. At 8 weeks 80 patients completed QoL questionnaires of which 74 were still on treatment.

Table 4: Effects of sertraline on patients' self-ratings of depression, anxiety and fatigue

	Adjusted mean scores at 4 and/or 8 weeks					Number of patients with major improvement			
	Sertraline n = 78	Placebo n = 84	Benefit	95% CI		P value*	Sertraline n = 78	Placebo n = 84	P value†
Depression									
CES-D	23.29	23.68	0.38	-2.66	3.42	0.81	3	6	0.33
HADS-D	24.05	25.44	1.39	-2.18	4.96	0.45	1	4	0.21
Pt-DATA	19.13	21.11	1.98	-3.78	7.75	0.50	18	13	0.43
Anxiety									
HADS-A	23.85	25.81	1.96	-1.56	5.47	0.28	6	3	0.50
Pt-DATA	21.74	22.62	0.89	-4.47	6.24	0.75	15	14	1.00
Fatigue									
FACT-F	42.90	43.20	0.30	-4.29	4.89	0.90	8	3	0.21
Pt-DATA	49.61	51.07	1.47	-4.57	7.51	0.63	16	17	0.85

* Generalised Estimating Equation

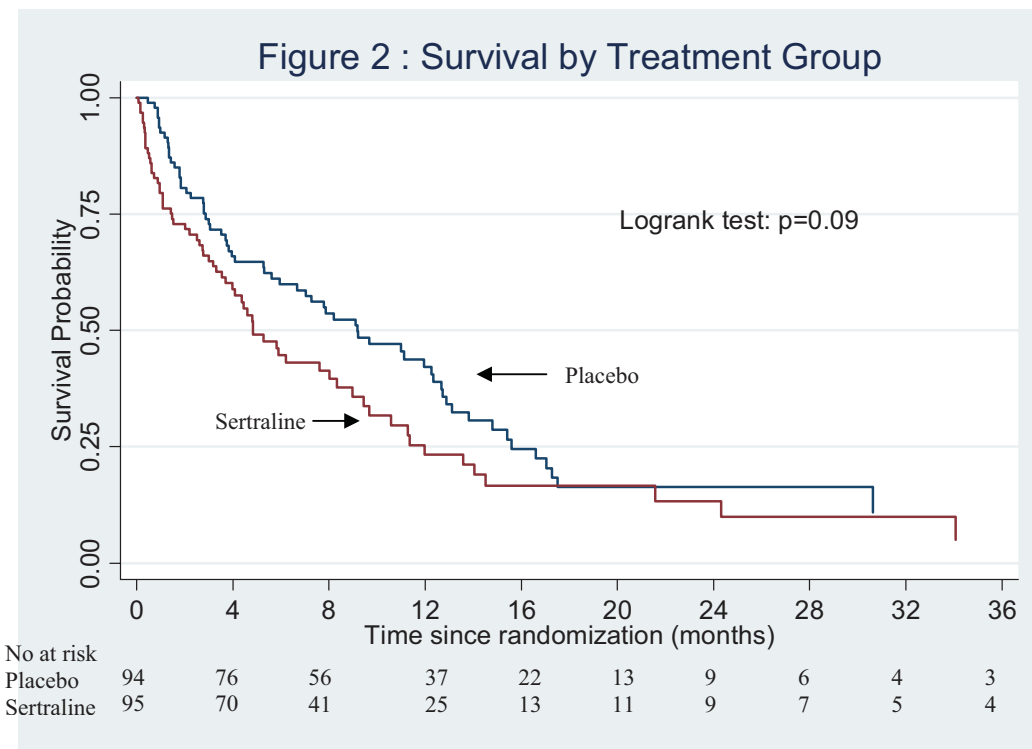
† Fisher's Exact Test

From the above table it is clear that sertraline has little effect on self-ratings of depression, anxiety or fatigue, with no significant differences between groups at 4 and 8 weeks. For example, in the sertraline group 3 patients have major improvement

according to CES-D and 6 patients in placebo group. Also for anxiety according to the HADS-A patients in the sertraline group score on average 1.96 points higher than placebo patients, but this improvement is not statistically significant ($p=0.28$).

95% CI's for every outcome measure excluded the minimum clinically important benefit of 10 points on a 100-point scale.

Figure 2: Survival by treatment group



At the final analysis ($n = 189$, median follow-up 19 months, range = 12 – 36 months), overall survival did not differ significantly between treatment groups (unadjusted hazard ratio 1.34 [CI: 0.95- 1.9], log-rank $p = 0.09$, Figure 2). Overall, 128 patients died (Figure 1).

Table 5 shows the results of univariable and multivariable analysis examining the association between baseline covariates and survival. In univariate analysis out of 22 covariates (excluding sertraline) only 12 were found significant and considered for

multivariable analysis. From the 13 covariates (with sertraline forced) entered into the backward elimination procedure, 6 were remained.

Table 5: Factors associated with survival in Cox's proportional-hazards model

Risk factors*	n (%)	Univariate Cox†			Multivariate Cox †				
		HR	95% CI		p-value	HR	95% CI		p-value
Sertraline	95 (50)	1.34	0.95	1.90	0.096	1.31	0.90	1.91	0.15
Age > 65	92 (49)	1.26	0.89	1.79	0.19				
Male	111(59)	1.47	1.02	2.13	0.04				
Liver or brain metastatic disease	65 (34)	1.63	1.13	2.36	0.01	1.64	1.11	2.41	0.01
Time from initial diagnosis to adv disease <9 month	94 (50)	1.42	1.00	2.01	0.05				
Primary Site: Lung	29 (15)	2.14	1.38	3.32	0.001	2.43	1.54	3.83	<0.01
Baseline treatment:									
Opioids	49 (26)	2.05	1.39	3.03	<0.01	1.97	1.29	2.99	<0.01
Steroids	21 (11)	1.45	0.87	2.42	0.16				
Previous/Current chemotherapy	156 (83)	1.84	1.12	3.04	0.02	1.99	1.17	3.40	0.01
Baseline bloods:									
Haemoglobin <12.3 g/L	94 (50)	1.58	1.11	2.24	0.011				
Lymphocytes <1.5 x10 ⁹ /L	99 (52)	1.43	1.01	2.02	0.045	1.50	1.04	2.16	0.03
Albumin <38 g/L	92 (49)	1.44	1.02	2.04	0.040				
ALP > 101 U/L	96 (51)	2.15	1.50	3.06	<0.01	2.31	1.59	3.36	<0.01
CRP > 10mg/L	101(53)	1.99	1.39	2.85	<0.01				
Creatinine > 74µmol/L	95 (50)	0.93	0.65	1.31	0.67				
Bilirubin > 9 mmol/L	92 (49)	1.06	0.75	1.51	0.73				
ECOG PS: 2	41 (22)	1.26	0.82	1.93	0.30				
KPS 70 or worse	46 (24)	1.61	1.08	2.41	0.02				
Body Weight < 76	95 (52)	1.31	0.92	1.88	0.13				
QOL:									
CES-D > 14	95 (51)	1.01	0.71	1.44	0.95				
FACT-F >23	93 (50)	1.04	0.73	1.47	0.84				
HADS-A > 5	95 (51)	1.06	0.75	1.51	0.74				
HADS-D > 5	80 (43)	1.10	0.77	1.57	0.61				

*Cutoffs for continuous variables were chosen to divide the sample into equal-sized groups.

†When calculating hazard ratios the expected best was the reference group (i.e., worst vs. best).

The adjusted hazard ratio for treatment effect (sertraline vs. placebo) changed little compared to the unadjusted result(adjusted HR = 1.31 [95% CI: 0.90-1.91], p = 0.15). Other factors which were associated with significant increased risk of death in multivariable analysis included: patients with liver or brain metastatic disease had 64% increased risk of death; patients with lung as the primary site had 2.4 times the risk of dying compared to those with other primary sites; patients on opioids or having chemotherapy at baseline had 2 times the risk of death compared to patients not on these

treatments. Lastly patients with lower lymphocytes ($<1.5 \times 10^9/L$) or higher ALP (>101 U/L) were associated with 50% and 131% increased risk respectively compared to patients in the other category.

Table 6 contains information for the 128 patients who died regarding the circumstances of their death and treatment received prior to the death. There was no difference in the number of deaths due to cancer progression between treatment groups (65 in sertraline group vs. 59 in placebo group, $p = 0.8$) or in the number of deaths occurring earlier than expected (6 vs. 6, $p = 1.0$).

However, fewer patients on sertraline than placebo were considered by their clinicians to have evidence of progressive cancer in the 3 months before death (88% vs. 98%, $p=0.03$). Half of the deaths in each group occurred while taking study drug or within 30 days of stopping it (34 in sertraline vs. 31 in placebo, $p = 0.6$). There were no differences in the rates of patients who received chemotherapy, radiotherapy or opioids since their last assessment prior to their death. No suicides were documented or suspected.

Table 6: Death timing, attribution and relation to treatments

	Sertraline	Placebo	P-value*
	(%)	(%)	
All deaths, N	67	61	
Death attributed to:			
Cancer	65 (97)	58 (95)	0.8
Anticancer treatment	0	0	
Cancer and anticancer treatment	0	1 (2)	
Other cause	2 (3)	2 (3)	
Place of death:			
Hospital	36 (55)	37 (63)	0.63
Hospice	12 (18)	9 (15)	
Nursing home	1 (1)	2 (3)	
Home	13 (20)	8 (14)	
Other	0	0	
Unknown	4 (6)	3 (5)	
Disease progression evident:			
Yes	58 (88)	58 (98)	0.03
No	6 (9)	0	
Unknown	2 (3)	1 (2)	
Died earlier than expected:			
Yes	6 (9)	6 (10)	1.0
No	57 (86)	53 (88)	
Unknown	3 (5)	1 (2)	
Relationship to study drug:			
On study drug	24 (36)	18 (30)	0.60
30 days or less after stopping drug	10 (15)	13 (21)	
>30 days after stopping study drug	33 (49)	30 (49)	
Relationship to anticancer treatment:			
Chemotherapy since last assessment	8 (15)	9 (20)	0.60
Radiotherapy since last assessment	5 (9)	4 (9)	1.0
Relationship to supportive treatment:			
Regular opioids since last assessment	27 (68)	21 (70)	1.0

*Fisher's exact test, unknown category excluded from calculation of p-value.

Per-protocol analysis: This analysis includes only those patients who received treatment so that a valid assessment can be made to ascertain whether the treatment is related to the occurrence of adverse events. For example, the active treatment may have side effect such as nausea. So, the per-protocol analysis includes only patients who took treatment so that this can be assessed accurately.

Table 7 details the frequency and severity of adverse events experienced by the patients in the two treatment groups. The frequency and severity of most adverse events were similar in both groups. Grade 2 or 3 vomiting was more common in sertraline group, whereas, mild oedema was more common in the placebo group.

Table 7: Adverse events: Worst grade experienced*† (%)

Grade	Sertraline (n = 91)					Placebo (n = 94)					P-value‡
	0	1	2	3	4	0	1	2	3	4	
Nausea	39	21	23	8	0	35	37	15	7	0	0.81
Vomiting	59	11	12	9	0	62	22	8	2	0	0.42
Diarrhoea	63	16	6	6	0	65	20	5	4	0	0.87
Constipation	51	24	8	6	2	43	32	17	2	0	0.29
Hyponatremia	77	12	0	2	0	73	17	0	4	0	0.22
Oedema	74	10	6	1	0	62	24	7	1	0	0.03
Thrombosis/ embolism	87	1	0	3	0	89	0	0	3	2	0.74
Headache	62	19	8	2	0	68	17	9	0	0	0.52
Confusion	75	9	4	2	1	82	9	3	0	0	0.31
Seizures	91	0	0	0	0	93	1	0	0	0	0.33
Depressed level of consciousness	75	11	3	2	0	77	8	6	2	1	0.84

*NCI CTC V2 grading scale

†Using events reported during assessments performed up to the assessment following the treatment termination date plus 30 days.

‡ Mann-Whitney U test

Table 8 details the worst toxicity levels reached for patients in each treatment group. Only some minor differences were observed between the sertraline and placebo group. For example, for creatinine, more patients in the sertraline group experienced grade I or II toxicity; but this difference is not statistically significant.

Table 8: Worst toxicity levels reached*† (%)

Blood test	Sertraline					Placebo					P-value‡
	0	1	2	3	4	0	1	2	3	4	
WCC	67	8	10	3	1	70	10	10	4	0	0.95
Lymphocytes	35	9	28	17	0	39	7	36	12	0	0.61
Hemoglobin	21	42	22	4	0	25	44	19	5	1	0.67
Platelets	60	25	2	2	0	65	20	6	3	0	0.99
Creatinine	67	14	7	0	0	79	13	2	0	0	0.15
Bilirubin	76	6	4	0	0	75	8	5	5	0	0.13
Serum albumin	46	19	20	2	0	36	32	22	3	0	0.15
Serum sodium§	47	35	0	6	0	49	34	0	10	1	0.64
AST	58	21	5	0	0	64	15	5	6	1	0.83
ALT	64	20	2	2	0	73	15	2	2	1	0.42
γGT	32	22	17	13	3	31	20	22	16	4	0.43
ALP	41	31	10	6	0	38	34	15	6	0	0.41

*NCI CTC V2 grading scale

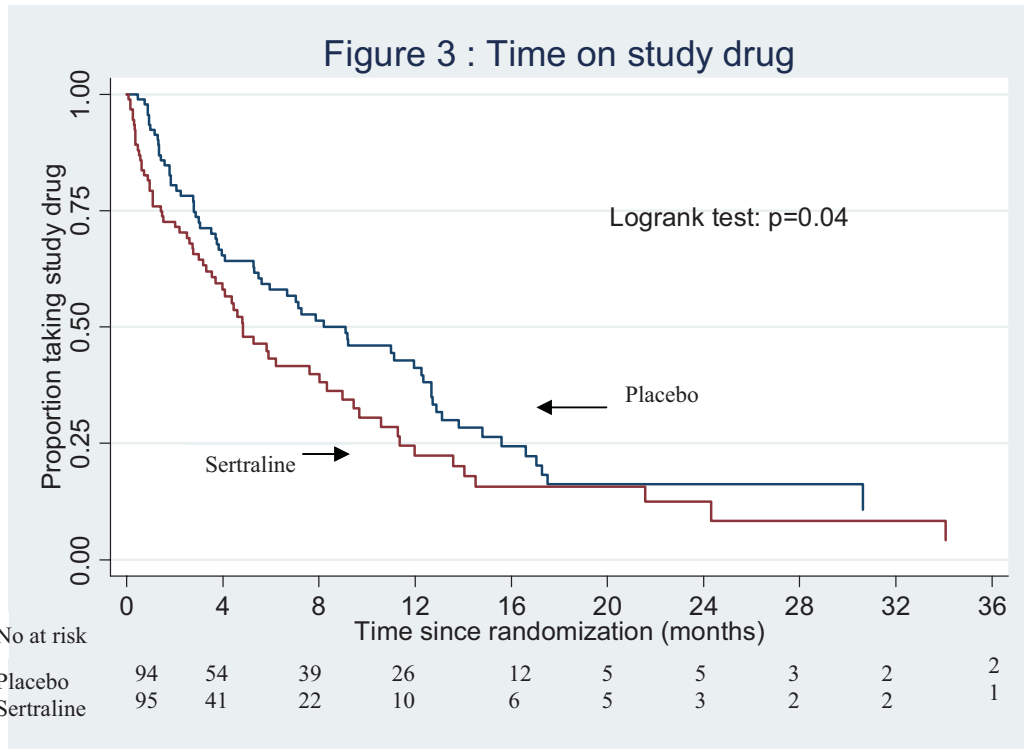
†Using laboratory measurements (up to 52 week assessments only) performed up to the treatment termination date plus 30 days and additionally the first laboratory test results done after this date.

‡ Mann-Whitney U test

§Grading system excludes grade 2.

Figure 3 shows the Kaplan-Meier curve for time to treatment discontinuation according to randomised treatment. Sertraline was discontinued earlier and more often than was placebo. The HR for discontinuing treatment for sertraline is 1.44 compared to placebo [95% CI: 1.02 to 2.04, log-rank p value = 0.04].

Figure 3: Time on study drug



Conclusion

Sertraline had no significant effect on depression (assessed by CES-D, HADS-D, Pt-DATA-Form), anxiety (assessed by HADS-A, Pt-DATA-A) or fatigue (assessed by FACT-F, Pt-DATA-F).

The interim analysis suggested a statistically significant ($2p=0.04$) adverse effect of sertraline on overall survival. This effect became less apparent with more patients and follow-up; as in the final analysis there was no longer a significant difference in survival time between the two treatment arms. Required sample size for the study was 400 patients (200 per group) to give over 90% power. Where as the interim analysis was conducted on 150 patients. Consequently this finding in the interim analysis was most likely a chance finding or due to chance imbalances between the two treatment arms. The estimated effect of sertraline on overall survival, from the final analysis, in this trial might have been biased by early stopping of the trial; the true effect would probably even be closer to no effect.

The difference in overall survival between groups at the first interim analysis did not reach the pre-specified rule for stopping ($2p=0.003$), but the independent safety and data monitoring committee believed that greater prudence was warranted for possible harm than for benefit, since survival time was significantly shorter (at the $\alpha = 0.05$ level of significance) in the sertraline arm. As a result the trial was suspended pending additional follow-up. The trial was closed because of futility reasons; there was no chance of a clinically important benefit of sertraline on QoL or survival. It was not closed because of concerns about adverse effects on survival or any harm. There was no chance of getting a significant benefit of treatment even if the trial continued until the original sample size was achieved. Also the recruitment rate was unacceptably slow.

There was no evidence to suggest that sertraline was associated with adverse effects that would decrease survival. Sertraline should continue to be used in patients with major depression however there is no indication for patients with minor depression.

The major strengths of the study were: double-blind, randomized design; use of validated outcome measures and enrolment of a broad cross-section of patients with advanced cancer. Compliance with completion of questionnaires (low missing data) and with study treatment was excellent. It was a high quality trial with very complete data. Results are generalisable to patients with all kinds of cancer. Therefore important benefits of sertraline in these patients are unlikely to have been missed out.

Imprecise definition of the study population was an important limitation of the study. The diagnosis of major depression was the main exclusion criteria, but this judgment was arbitrary and left to the responsible oncologist. But this is the reality in clinical practice anyway.

The lowest recommended dose of sertraline was used to avoid side effects. We doubt that a higher dose or a different anti-depressant may have been more effective. However this possibility cannot be ruled out.

We postulated that improvement in aspects of QoL (depression, anxiety and fatigue) would increase survival. This remains untested because symptoms of QoL were not improved by this trial. This causal assumption may be flawed anyway. Earlier small trials which demonstrated this were not confirmed by larger trials.

The study did not find any significant effect of improving depression in cancer patients due to the treatment. The study needed 440 patients to have enough power to detect a clinically significant benefit of sertraline on QoL. However, analysis based on the 189 patients randomised revealed that the trial should be closed due to futility reasons as there was no chance of obtaining a clinically significant effect. There is another issue with the definition of major depression.

As per the general principle, if a treatment really works for improving an outcome, the effect would be more obvious if the study is conducted on patients with severe illness. Despite the possible inclusion of patients with major depression into the trial, due to the arbitrary nature of the exclusion criteria, there was still no benefit demonstrated by sertraline on improving quality of life.

Abbreviations

HR	Hazard Ratio
QoL	Quality of life
CES-D	Centre for Epidemiologic Studies- Depression
HADS	Hospital Anxiety and Depression Scale
FACT	Functional Assessment of Cancer Therapy
Pt DATA	Patient Disease and Treatment Assessment Form
KPS	Karnofsky Performance Status
ECOG	Eastern Cooperative Oncology Group

References

- ¹ Australian Institute of Health and Welfare. Cancer in Australia 1997: Incidence and mortality data for 1997 and selected data for 1998 and 1999. Canberra, 2000.
- ² Derogatis LR et al. The prevalence of psychiatric disorders among cancer patients. JAMA 1983; 249: 751-7.
- ³ Plumb M, Holland J. Comparative studies of psychological function in patients with advanced cancer. II: Interviewer-rated current and past psychological symptoms. Psychosomatic Med 1981; 43:243-54.
- ⁴ Passik SD, Dugan W, McDonald MV, Rosenfeld B, Theobald DE, Edgerton S. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol 1998; 16: 1594-1600.
- ⁵ Portenoy RK, Thaler HT, Kornblith AB et al. Symptom prevalence, characteristics, and distress in a cancer population. Qual Life Res 1994; 3: 183-9.
- ⁶ Tannock IF, Osoba D, Stockler M, Ernst S, Neville AJ, Moore MJ, Armitage GR, Wilson JJ, Venner PM, Coppin CML, Murphy KC. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative endpoints. J Clin Oncol 1996; 14: 1756-64.
- ⁷ Stockler M, Osoba D, Corey P, Goodwin P, Tannock IF. Convergent, discriminative and predictive validity of the prostate cancer specific quality of life instrument (PROSQOLI): assessment and comparison with analogous scales from the EORTC QLQ-C30 and a trial specific module. Journal of Clinical Epidemiology 1999; 52 (7):653-666.
- ⁸ Cella D. Factors influencing quality of life in cancer patients: anaemia and fatigue. Sem Oncol 1998; 25(3): 43- 6(Suppl 7).
- ⁹ Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? Supp Care Cancer 1998; 6:101-8.
- ¹⁰ Van der Linden G et al. Fatigue and psychiatric disorder: different or the same? Psych Med 1999; 29: 863-8.
- ¹¹ Coates A, Gebiski V, Signorini D et al. Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. J Clin Oncol 1992; 10: 1833-8.

- ¹² Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989; 2: 888-891.
- ¹³ Kogon MM, Biswas A, Pearl D, Carlson RW, Spiegel D. Effects of medical and psychotherapeutic treatment on the survival of women with metastatic breast carcinoma. *Cancer* 1997; 80:225-30.
- ¹⁴ Fawzy FI, Fawzy NW et al. Malignant melanoma. Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Arch Gen Psych* 1993; 50: 681-689.
- ¹⁵ Goodwin PJ et al. Lessons learned from enrollment in the BEST study - a multicenter, randomized trial of group psychosocial support in metastatic breast cancer. *J Clin Epidemiol* 2000; 53: 47-55.
- ¹⁶ Gill D, Hatcher S. Antidepressants for depression in people with physical illness. In: *The Cochrane Library*, 2000.
- ¹⁷ Razavi D, Allilaire J-F, Smith M et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. *Acta Psychiatr Scand* 1996; 94: 205-210.
- ¹⁸ Costa D et al, Mogoa I, Toma T. Safety of mianserin in the treatment of depression of women with cancer. *Acta Psychiatr Scand* 1985; 72: 85-92.
- ¹⁹ Van Heeringen K, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. *Br J Psychiatr* 1996; 169:440-3.
- ²⁰ Holland JC, Romano SJ, Heiligenstein JH, Tepner RG, Wilson MG. A controlled trial of fluoxetine and desimpramine in depressed women with advanced cancer. *Psycho-Oncol* 1998; 7: 291-300.
- ²¹ Hickie IB, Davenport TA, Naismith SL, et al. , Treatment of common mental disorders in Australian general practice. *Med J Aust* 2001; 175 Suppl Jul 16: S25-S30.
- ²² Cancer Therapy Evaluation Program. Common toxicity criteria, version 2.0. Bethesda, Md.: National Cancer Institute, 1998.
- ²³ Kleinbaum DG, Klein M. *Survival Analysis A Self-Learning Text*, Second Edition, 2005, 57-68.
- ²⁴ Tannock IF, Osoba D, Stockler M, Ernst S, Neville AJ, Moore MJ, Armitage GR, Wilson JJ, Venner PM, Coppin CML, Murphy KC. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative endpoints. *J Clin Oncol* 1996; 14: 1756-64.

²⁵ Stockler M, Osoba D, Corey P, Goodwin P, Tannock IF. Convergent, discriminative and predictive validity of the prostate cancer specific quality of life instrument (PROSQOLI): assessment and comparison with analogous scales from the EORTC QLQ-C30 and a trial specific module. *Journal of Clinical Epidemiology* 1999; 52 (7):653-666.

²⁶ Stockler M, Osoba D, Goodwin PJ, Corey P, Tannock IF. Responsiveness to change in health-related quality of life in a randomized trial: a comparison of the prostate cancer specific quality of life instrument (PROSQOLI) with analogous scales from the EORTC QLQ-C30 and a trial specific module. *J Clin Epidemiol* 1998; 51:137- 45.