Title: Does depression treatment improve the survival of depressed cancer patients? A long-term follow-up of participants in the SMaRT Oncology-2 and 3 trials.

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SUMMARY

Background

Comorbid major depression has been associated with worse survival in patients with cancer. However, we do not know if treating depression improves survival. In the SMaRT Oncology-2 (good prognosis cancers) and SMaRT Oncology-3 (lung cancer, a poor prognosis cancer) trials, we found that a depression treatment programme, Depression Care for People with Cancer (DCPC), was highly effective in reducing comorbid major depression. In this analysis, we aimed to determine whether DCPC also had an effect on survival.

Methods

We obtained long-term data on deaths (all causes) in the 642 SMaRT Oncology-2 and 3 trial participants, censored at July 31, 2015, and analysed survival as a trial outcome. We estimated unadjusted hazard ratios (HRs) for each trial using Cox regression, and pooled the log HRs in a fixed-effects meta-analysis.

Outcomes

We followed up SMaRT Oncology-2 and SMaRT Oncology-3 participants for a median of one and five years respectively. 135/500 (27%) SMaRT Oncology-2 participants and 114/142 (80%) SMaRT Oncology-3 participants died within this period. We found no statistically significant effect of DCPC on survival in the total follow-up period for either trial (SMaRT Oncology-2 HR 1·016, 95% CI 0·72 to 1·42, p=0·93; SMaRT Oncology-3 HR 0·82, 95% CI 0·56 to 1·18, pooled HR 0·92, 95% CI 0·72 to 1·18, p=0·28).

Interpretation

DCPC is highly effective in improving depression and quality of life in depressed cancer patients, but does not have a statistically significant effect on survival.

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INTRODUCTION

There has been longstanding controversy about whether psychiatric and psychological treatments improve the survival of cancer patients. Two influential trials, published more than 20 years ago suggested that they did.[1,2] However, recent systematic reviews of this topic have been inconclusive, finding small effects only in subgroups of patients or at specific times after cancer diagnosis.[3,4] Major shortcomings in the trials conducted to date include a lack of specific targets for the psychiatric treatments and a corresponding heterogeneity in the psychiatric diagnoses of trial participants. There is therefore considerable uncertainty about the effect of psychiatric interventions on survival and a corresponding need to evaluate the effect of a clearly targeted psychiatric treatment in cancer patients who share a specific psychiatric diagnosis.

Major depression comorbid with cancer is a suitable specific psychiatric diagnosis to target. That is because it affects approximately 10% of cancer patients and has been round in multiple studies to be associated with worse survival.[5-8] However, despite the association with worse survival, we are not aware of any trials that have aimed to find out if giving treatment for depression (pharmacological, psychological or both) to depressed patients with cancer improves their survival?

In this paper, we aim to determine the effect of a multi-component depression treatment programme called Depression Care for People with Cancer (DCPC) on the survival of patients with cancer.[9] Between 2008 and 2011, we conducted two randomised controlled trials (Symptom Management Research Trials; SMaRT Oncology-2 and SMaRT Oncology-3) comparing DCPC with usual care in patients with good prognosis and poor prognosis cancers, all of whom had comorbid major depression, and found that DCPC was much more effective than usual care in improving depression.[10,11] DCPC also improved patients' symptoms, functioning and quality of life. We aimed to find out if DCPC also improved participant survival. In order to do we obtained long-term data on deaths (from all causes) of SMaRT Oncology-2 and 3 trial participants, and analysed survival as a trial outcome.

METHODS

The trials: SMaRT Oncology-2 and 3

The published protocols and trial reports for SMaRT Oncology-2 and 3 describe the trial methods, including the trial treatments in detail.[10-13] In brief, these were both two-arm parallel group randomised controlled trials which compared DCPC with usual care in patients with cancer and comorbid major depression.

DCPC is a manualised, multicomponent (with both pharmacological and psychological components), collaborative care treatment that is delivered systematically by a team of cancer nurses and psychiatrists in collaboration with oncologists and primary care physicians.[9] DCPC was adapted in SMaRT Oncology-3 to meet the needs of patients with a lung cancer, a poor prognosis cancer (as Depression Care for People with Lung Cancer, DCPLC to achieve a rapid treatment response and to enable patients to continue treatment despite physical deterioration.[11] Usual care was provided by the participants' own primary care physician and oncology team in both trials. We registered the trials with Current Controlled Trials, numbers ISRCTN40568538 and ISRCTN75905964.

We recruited 642 participants to these two trials from three cancer centres in Scotland, UK and their associated clinics. We recruited five hundred patients with good prognosis cancers (predicted survival ≥12 months estimated by their cancer specialist) and comorbid major depression to SMaRT Oncology-2 between 12th May 2008 and 13th May 2011. We recruited one hundred and forty-two patients with lung cancer (predicted survival ≥3 months) and comorbid major depression to SMaRT Oncology-3 between 5th January 2009 and 9th September 2011. In both trials participants were randomly allocated (1:1) to either DCPC or usual care.

This further analysis of the trial data to include survival data was approved by the Scotland A Research Ethics Committee (08/MRE00/23; 08/MRE00/95) and the NHS Scotland Privacy Advisory Committee. At the time of original trial enrolment, participants gave written consent for us to obtain follow-up information from their medical records.

Procedures

We obtained mortality data on trial participants (dates and causes of death) from the National Records of Scotland database on 31st July 2015. We did this by sending a minimal dataset (each participant's trial number, name, date of birth, gender, Community Health Index (CHI) number, postcode, and date of randomisation) securely to the Information Services Division of NHS Scotland for records linkage.

Statistical analysis

We calculated time to death (from any cause) from the date of each participant's trial enrolment (randomisation). We censored participants who: (a) had left Scotland (at their date of emigration); (b) were not known to have died or to have emigrated (at the latest date on which data were available, which was July 31, 2015). We analysed the two trials separately. We used log-rank tests to compare the distribution of time to death in the trial arms, plotted Kaplan-Meier survival estimates for the trial arms and estimated unadjusted hazard ratios (HRs) for each trial using Cox regression. The Cox model estimates the ratio of the instantaneous risks (termed hazards) of death between the two arms of a trial, assuming that this ratio does not change over time (proportional hazards). We checked for violations of the assumption by calculating scaled Schoenfeld residuals and plotting them against duration of follow up. If the assumption is correct the slope of a generalized least squares regression line in this graph should be zero.[14] Finally, we pooled the log HRs from the two trials using the inverse-variance method in a fixed-effects meta-analysis to report a combined HR. We performed all statistical analyses using Stata v14 (StataCorp, College Station, TX, USA).

Role of the funding source

The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We obtained data on all trial participants. Table 1 shows their demographic and clinical characteristics. We also obtained follow up data on SMaRT Oncology-2 participants (until the time of their death or to July 31, 2015 if that was sooner) for a median of 5·1 years (maximum 7·1 years) and on SMaRT Oncology-3 participants for a median of 1·2 years (maximum 6·5 years).

[Table 1 here]

135/500 (27%) SMaRT Oncology-2 participants and 114/142 (80%) SMaRT Oncology-3 participants had died during the follow up period. The majority of deaths were cancer-related. None of the deaths had been attributed to suicide (see Table 2).

[Table 2 here]

In SMaRT Oncology-2 we found no statistically significant difference in survival between DCPC and usual care arms of the trial (p=0·93, log rank test). Inspection suggested that the Kaplan-Meier survival curves diverged slightly at around one year post-randomisation in favour of usual care, and crossed over at five years in favour of DCPC (see Figure 1); the Schoenfeld residual plot also suggested the HR may decrease over follow-up time (not shown). However, the analogous test for a non-constant hazard ratio was not statistically significant (p=0.066). The hazard ratio from the Cox proportional hazards model was 1·016 with the 95% confidence interval (0·72 to 1·42), p=0·93. This finding is consistent with both moderately positive and negative effect of DCPC on survival.

[Figure 1 here]

In SMaRT Oncology-3 we again found no statistically significant difference in survival between the two arms of the trial (p=0·28, log rank test). Whilst inspection suggested a steeper decline in survival probability in the usual care arm between one and two years

post-randomisation, and a separation in the Kaplan-Meier survival curves thereafter (see Figure 1), the hazard ratio of 0·82 (in favour of DCPC) with a 95% CI extending from 0·56 to 1·18 (p=0·28) again reflects substantial uncertainty in the estimate. It is also consistent with both a positive effect and a modest negative effect of DCPC on survival. There was no statistical evidence of non-proportionality in this hazard ratio (p=0·71).

Combining the two trials yielded a pooled hazard ratio for survival of 0·92 (95% CI 0·72 to 1·18, p=0·51). This confidence interval is again consistent with moderate effects of DCPC on survival in both directions. It is also notable that this finding was not substantially different in a sensitivity analysis that included only those deaths attributed to cancer.

DISCUSSION

Main findings

This is the first report to investigate the effect on survival of a depression treatment programme (DCPC) for cancer patients with a diagnosis of comorbid major depression. Although DCPC has been found to be highly effective in improving depression,[10,11] we found no statistically significant evidence that it also prolongs survival.

Strengths and limitations

This finding must be considered in the context of the strengths and limitations of the study. The strengths include the comparison of randomised groups, recruitment into the trials by systematic screening, a large observed effect of treatment on depression and high degree of completeness of follow up data. The study also had limitations: First, whilst the size of the trials analysed was sufficient to address the primary research question, it offered only limited power to detect a small but potentially clinically relevant effect on survival. We observed 135 deaths in SMaRT-2 and 114 deaths in SMaRT-3 at follow-up. This number of deaths provided 80% statistical power to detect a pooled HR of 0·70 at 5% statistical significance; a large but plausible effect. It is also worth noting that the detection of a smaller effect on survival would require very large numbers. For example, to have 80% statistical power to detect a more modest HR of 0·80, a new trial with a similar death rate at follow up, would need to recruit more than 1,500 patients. Second, although we were able to obtain long-term mortality data, we were not able to follow all trial participants to their date of death. Whilst this limitation makes us potentially unable to detect longer-term effect of depression treatment on survival, it seems unlikely that any long-term effect would be greater than that observed sooner after treatment for depression was given. Third, as SMaRT Oncology-2 and 3 only included participants who had an estimated prognosis of at least 12 months and at least three months respectively, our ability to detect an effect in patients with a very poor cancer prognosis was limited. Fourth, the trials (in particular SMaRT Oncology-2) included participants with heterogeneous cancer diagnoses who had various cancer treatments; the limited power of our analysis did not allow us to explore whether the effect of DCPC on survival was different for patients with different cancer types receiving differing cancer treatments. A final limitation is that our analysis compared

survival between trial arms; that is between participants randomly allocated to receive either DCPC or usual care, following the intention to treat principle. This design is a notably robust method for comparing the effect of DCPC with usual care. However, it does not address the related, but different question, of whether getting better from depression is associated with increased survival. This requires a different type of analysis of the data that is not based on the randomised comparison of treatments. We will report on this analysis elsewhere.

Previous studies

We are not aware of any previously published trials that have specifically addressed whether delivering depression treatment to cancer patients with comorbid major depression improves their survival. Of some relevance is a secondary analysis of a trial in which early palliative care for patients with lung cancer was found to improve survival, did not find that the survival effect was mediated by improving depression.[15,16]

An association of comorbid major depression with worse survival has also been found in patients suffering from medical conditions other than cancer, most notably heart disease.[17-21] It is therefore of interest that trials of depression treatment in patients with heart disease and comorbid depression have also failed to find good evidence of improved survival.[22-25]

Conclusion

In conclusion, major depression is a common and important problem in patients with cancer. It is associated with both reduced quality of life and worse survival. In the SMaRT Oncology 2 and 3 trials of depression treatment, we observed a strong effect on depression and quality of life, but no convincing evidence of an effect on survival. Despite the lack of effect on length of life, the beneficial effect of treatment of depression on quality of life provides sufficient reason to make this an important part of cancer care.

CONTRIBUTORS

All authors contributed to study design and data interpretation. AM and CF designed and conducted the statistical analysis. AM, SP, JW, CF and MS drafted the paper and all other authors provided critical revision of the manuscript.

CONFLICTS OF INTEREST

We declare that we have no conflicts of interest.

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RESEARCH IN CONTEXT

Evidence before this study

Recent systematic reviews have suggested that psychiatric interventions might improve survival in some cancer patients. Studies have also found that comorbid depression in particular predicts worse survival. We were therefore interested in the determining the effect on survival of the treatment of comorbid major depression in cancer patients. We searched PubMed from 01/01/1900 to 01/01/2018 using the search terms cancer [Title] AND depress*[Title] AND surviv* [Title] AND trial* and found no papers reporting survival outcomes from randomised clinical trials of interventions for comorbid major depression in cancer patients.

Added value of this study

We compared the survival outcome of people with cancer and comorbid major depression given depression treatment, with that of those receiving only usual care in the SMaRT Oncology-2 and 3 trials. Whilst the treatment was highly effective in improving depression, we did not find statistically significant evidence that it also improved survival.

Implications of all the available evidence

There is no convincing evidence from clinical trials that treating comorbid depression in cancer patients has a substantial effect on their survival. This finding is consistent with findings in patients with cardiac disease. Much larger trials with long duration of follow up would be required to find out if there are modest but clinically significant effects on survival. Nonetheless, the evidence for a beneficial effect on quality of life already indicates the treatment of depression in people with cancer.

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Table 1: Characteristics of SMaRT Oncology-2 and SMaRT Oncology-3 trial participants

	SMaRT Oncology-2		SMaRT Oncology-3	
	DCPC (n=253)	Usual care (n=247)	DCPLC (n=68)	Usual care (n=74)
Age at trial enrolment (years)	56·6 (10·0)	56·1 (10·2)	63·6 (8·8)	63·9 (8·7)
Sex				
Women	227 (90%)	222 (90%)	44 (65%)	48 (65%)
Men	26 (10%)	25 (10%)	24 (35%)	26 (35%)
Primary cancer				
Breast	140 (55%)	131 (53%)	-	-
Gynaecological	57 (23%)	64 (26%)	-	-
Genito-urinary	13 (5%)	14 (6%)	-	-
Other	43 (17%)	38 (15%)	-	-
Non-small cell lung cancer	-	-	43 (63%)	50 (68%)
Small cell lung cancer	-	-	16 (24%)	14 (19%)
Other lung	-	-	9 (13%)	10 (14%)
Trial primary outcome				
Depression treatment response[1]	143 (62%)	40 (17%)	-	-
Average depression severity[2]	-	-	1·24 (0·64)	1·61 (0·58)
Follow up time in years (median, IQR)	5·0 (4·2, 5·8)	5·1 (4·3, 5·8)	1·3 (0·5, 4·2)	1·0 (0·6, 3·0)
Deaths	68 (27%)	67 (27%)	52 (76%)	62 (84%)
Emigrations	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Death rate per 100 person years	6·0	5·9	33·5	44·8

Data are mean (SD) or n (%) unless otherwise indicated. [1] 50% reduction on Symptom Check List-20 Depression subscale at 24 weeks. [2] Average depression severity (using Symptom Check List-20 Depression subscale) throughout the period of the participant's trial participation up to a maximum of 32 weeks.

Table 2: Primary causes of death in SMaRT Oncology-2 and SMaRT Oncology-3 trial participants

Primary cause of death	SMaRT Oncology-2 participant deaths		SMaRT Oncology-3 participant deaths	
	DCPC (n=68)	Usual care (n=67)	DCPC (n=52)	Usual care (n=62)
Cancer	55 (81)	63 (94)	43 (83)	55 (89)
Breast	19 (28)	27 (40)	0	0
Gynaecological	20 (29)	15 (22)	0	0
Genitourinary	4 (6)	6 (9)	0	0
Lung	0	3 (4)	43 (83)	51 (82)
Other[1]	12 (18)	12 (18)	0	4 (6)
Cardiovascular disease[2]	7 (10)	2 (3)	4 (8)	2 (3)
Respiratory disease	3 (4)	1 (1)	4 (8)	1 (2)
Other[3]	3 (4)	1 (1)	1 (1)	4 (6)

Data are n(%). [1] Haematological, upper gastrointestinal, colorectal, primary peritoneal, unspecified intestinal and cancer of multiple primary sites. [2] Myocardial infarction, chronic ischaemic heart disease, cerebrovascular disease, cardiac failure. [3] Obstructed inguinal hernia, sarcoidosis, acute pancreatitis, gastrointestinal haemorrhage, liver disease, sepsis.

Figure 1.