RESEARCH ARTICLE

Editorial Process: Submission:10/19/2022 Acceptance:08/05/2023

A 6-Month Open-Label Study of Vortioxetine among Cancer Patients with Major Depressive Disorder (MDD)

Chong Guan Ng[1]*, Aya Ahmed Abousheishaa[1], Sue Yin Low[2], Nor Zuraida Zainal[1], Kai Shin Thong[3], Azizul Bin Awaluddin[4], Tsui Huei Loo[5], Sapini Binti Yacob[6], Nik Ruzyanei Nik Jaafar[7], Nur Iwana Binti Abdul Taib[7], Nurul Ain Binti Mohamad Kamal[7], Fuad Ismail[8], Wan Zamaniah Wi[9]

Abstract

Objective: Vortioxetine is a monoaminergic drug with a novel multimodal mechanism of action. We investigated its efficacy on depressive symptoms, cognitive function, and quality of life among cancer patients.**Methods:** In this multicenter, open-label, single-arm, observational study, patients received flexible doses of Vortioxetine for a period of six months. All participants were assessed at baseline and scheduled for monitoring at weeks 2, 4, 8, 12, 16, 20, and 24. Depression severity was assessed using Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI) scale. The Perceived Deficiency Questionnaire (PDQ-5) assessed the perceived cognitive difficulties in concentration, executive functioning, and memory. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) was used to assess the patients' quality of life. Side effects of vortioxetine were monitored using the Antidepressant Side-Effect Checklist (ASEC). **Results:** Patients experienced a reduction in MADRS scores from 29.89 ± 5.997 at baseline to 11.59 ± 4.629 by Week 24. The PDQ-5 scores showed significant change from Week-4, whereas the EORTC role, emotional, and cognitive functioning scores showed a significant change from Week 2 onwards. CGI-Severity scores decreased from a baseline of 4.39 ± 0.746 to 2.41 ± 1.085 by Week 24. During the 24-Weeks of therapy, around three-quarters of the patients (73.3%) had one or more adverse events reported on the ASEC. The most frequently reported TEAEs were dry mouth, insomnia, somnolence, and headache, with more than a 30% incidence rate. **Conclusion:** Vortioxetine seems promising in the management of depression and enhancement of cognitive function and quality of life of cancer patients with Major Depressive Disorder.

Keywords: Antidepressants- oncology- depression- quality of life- cognitive dysfunction

Asian Pac J Cancer Prev, **24 (8)**, 2583-2591

Introduction

Depression is a leading cause of global disease burden and is one of the largest contributors to non-fatal health loss and worldwide disability (Friedrich, 2017). It is especially prevalent in individuals with chronic diseases such as cancer and is often associated with aggravated existing pain, lower quality of life, reduced treatment success (Doan et al., 2015; Friedrich, 2017), and poorer prognosis and higher mortality (Fann et al., 2008; Niedzwiedz et al., 2019; Sotelo et al., 2014). Major depressive disorder (MDD) has also been associated with cognitive dysfunction (Lin et al., 2014) and functional impairment (Hybels et al., 2016), which significantly compounds the effect of cancer and further compromises the quality of life.

Despite the high susceptibility and prevalence of depressive disorders among cancer patients, depression is often underdiagnosed and understudied within this population. This is due in part to the overlap of depressive symptoms and common somatic symptoms in cancer, such as weight loss, sleep disturbances and fatigue, low

*[1]Department of Psychological Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. [2]Department of Psychology, Faculty of Behavioural Sciences, HELP University, Kuala Lumpur, Malaysia. [3]Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Selangor, Malaysia. [4]Department of Psychiatry and Mental Health, Hospital Putrajaya, Kuala Lumpur, Malaysia. [5]Department of Psychiatry, Hospital Raja Permaisuri Bainun, Perak, Malaysia. [6]Department of Psychiatry and Mental Health, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia. [7]Department of Psychiatry, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. [8]Department of Radiotherapy and Oncology, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. [9]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. *For Correspondence: chong_guan@um.edu.my. Aya Ahmed Abousheishaa and Low Sue Yin have equal contribution in this study.*

energy, and cognitive impairment (Niedzwiedz et al., 2019). Furthermore, research suggests that there may be bidirectional influences between pain, cognitive dysfunction, and depression: such that chronic pain and cognitive dysfunction may lead to higher risks of depression while depression may amplify the pain severity as well as exacerbate existing cognitive dysfunctions (Chochinov, 2001; Di Iulio et al., 2019). Cognitive impairments are a clinically significant problem for cancer patients, especially during chemotherapy, and its effects may last long after treatment and remission (Di Iulio et al., 2019).

While various antidepressants effectively treat depression within the general population irrespective of age (Katona et al., 2012; McIntyre et al., 2014), MDD remains challenging to treat among those with cancer. This is especially true in balancing potential adverse effects resulting from antidepressants, already taxing cancer treatments, and any potential drug interactions that may arise. Over the last few decades, new classes of antidepressants with fewer adverse effects have emerged. Of these, vortioxetine, for which a dearth of research exists within oncological settings, is of particular interest. Vortioxetine is a monoaminergic drug with a novel multimodal mechanism of action. It functions by combining the modulation of the 5-HT receptors (an agonist of 5-HT1A; partial agonist of the 5-HT1B; antagonist of the 5-HT3, 5-HT1D, and 5-HT7) and the inhibition of serotonin reuptake transporters (SERT). While long-term or chronic therapy with early-approved antidepressants often desensitizes 5-HT1A at the presynaptic neuron, creating a negative feedback loop that eventually reduces their anti-depressive effects, vortioxetine is an agonist of 5-HT1A, which may instead accelerate and maintain antidepressant effects (D'agostino et al., 2015).

More notably, vortioxetine is currently the only FDA-approved pharmacological agent for the treatment of MDD through the direct targeting of cognitive dysfunction (Lundbeck, 2018). This unique clinical feature has been demonstrated in both preclinical and clinical studies, whereby it exerts additional efficacy in improving cognitive function in individuals with depression independent of its effects as an antidepressant (Lundbeck, 2018; Mahableshwarkar et al., 2015; McIntyre et al., 2014; Smith et al., 2018). Its combined effect on SERT and 5-HT receptors has been suggested to significantly improve attention, executive function, learning, processing speed, and memory (Lundbeck, 2018) and enhance neurogenesis and plasticity-promoting effects (Bennabi et al., 2019). In head-to-head trials with escitalopram, vortioxetine more significantly improved short-term memory, attention, and processing speed parameters and had a greater positive influence on social, working, and total functioning (Levada and Troyan, 2019). Similarly, direct comparison studies of vortioxetine and duloxetine found that vortioxetine more greatly enhanced all measured parameters of cognitive function (Katona et al., 2012; Mahableshwarkar et al., 2015).

In addition to the above, vortioxetine demonstrates an efficacy profile comparable to that of other effective treatments of MDD and a favorable safety profile (Connolly and Thase, 2016; D'agostino et al., 2015; Nomikos et al., 2017), characterized by a lower incidence of sexual dysfunction and sleep disruption (Sanchez et al., 2015). Due to its relatively long half-life, vortioxetine is also generally well-tolerated with a low level of discontinuation symptoms in short-term and long-term clinical studies (Mahableshwarkar et al., 2015; McIntyre et al., 2014; Sanchez et al., 2015). Vortioxetine has also demonstrated good tolerability among multi-morbid MDD patient populations on various concomitant medications (Nomikos et al., 2017). In terms of pharmacokinetic drug interactions, vortioxetine has little to no effect on various cytochrome P450 (CYP) isoforms (Spina and Santoro, 2015), thus putting it at a major advantage compared to other widely-used antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline, and citalopram (Hemeryck and Belpaire, 2002).

As such, it is conceivable that vortioxetine could potentially be a viable or preferable treatment for depression in patients experiencing depressive episodes associated with cognitive dysfunction, such as those with cancer-related cognitive impairment. Hence the objectives of our study were to determine the efficacy of vortioxetine on depression and cognitive function and to elucidate its potential effects on quality of life in patients with cancer of any origin.

Materials and Methods

Study Design

This was an open-label, single-arm, observational study conducted in six public hospitals across Malaysia over a period of twenty months. Patient recruitment started on 1st November 2019 and lasted until 31st December 2020; follow-up continued for six months after that, following which the trial officially ended on 31st May 2021. Ethics approval was obtained from the Medical Research Ethics Committee at Universiti Malaya (UMMC MREC; 201972-7593) and the National Medical Research and Ethics Committee (MREC; NMRR-19-2850-50323). Furthermore, the trial protocol was registered at ClinicalTrials.gov (NCT04253678).

Patient recruitment was done at the psychiatry clinics of the included hospitals, following a consecutive sampling technique. Eligible patients received flexible doses of vortioxetine and were monitored closely during scheduled follow-up visits. Since the study was conducted during routine medical care, augmentation of treatment with chemotherapy and radiotherapy was permitted according to the attending physicians' best clinical judgment. If patients did not respond favorably to the drug treatment, they were withdrawn from the study and received standard care as per the discretion of their attending psychiatrist.

Study Participants

The study participants were outpatients aged 18 years and above with cancer of any origin and a primary diagnosis of MDD based on the DSM-IV-TR criteria.

At baseline screening, patients were administered the Montgomery- Åsberg Depression Rating Scale (MADRS), and a score of at least 20 was required for eligibility, indicating moderate to severe depression.

Patients were excluded if they demonstrated: (1) comorbid psychiatric disorders other than MDD, (2) active psychosis, (3) delirium, (4) medical instability, (5) cognitive deficits of causes other than cancer or primary/ secondary cerebral/cranial tumors.

Materials

Montgomery- Åsberg Depression Rating Scale (MADRS)

Depression severity at baseline and change across the study duration was assessed using MADRS. It consists of 10 items evaluating core symptoms of depression: (1) apparent sadness; (2) reported sadness; (3) tension; (4) reduced sleep; (5) reduced appetite; (6) concentration difficulties; (7) lassitude; (8) inability to feel; (9) pessimistic thoughts; (10) suicidal thoughts (Asberg et al., 1978; Montgomery and Asberg, 1979). Items are rated from 0 (no abnormality) to 6 (severe), with a maximum total score of 60. To ensure a high level of inter-rater reliability, all raters attended training in MADRS rating to address any concerns prior to study commencement.

Perceived Deficits Questionnaire -5 items (PDQ-5)

PDQ-5 is a 5-item self-report scale that assesses perceived cognitive difficulties in concentration, executive functioning, and memory. This brief version of the original 20-item PDQ has been adapted and validated for use in patients with MDD (Lam et al., 2018). The questionnaire estimates symptoms based on the past week, with each item rated on a scale of 0 to 3, where a higher score reflects greater severity of cognitive dysfunction.

Clinical Global Impression (CGI)

The CGI is used in clinical trials to provide a brief clinician's view of the patient's global functioning. The CGI is a one-item measure that consists of two components: (a) severity of clinical condition from 1 to 7 and (b) change from the initiation of treatment on a similar seven-point scale ranging from 1 (very much improved) to 7 (very much worse) (Guy, 1976). As such, CGI-I scores were measured from Week 2 to Week 24 and were not assessed at baseline.

EORTC QLQ-C30

This scale is a widely used clinical scale measuring the cancer-specific quality of life. It contains five functioning scales (physical, social, role, cognitive, and emotional functioning), eight symptom scales (fatigue, nausea/ vomiting, pain, dyspnea, sleep disturbances, appetite loss, constipation, and diarrhoea), financial impact, and overall quality of life. All scale scores are linearly converted to a range from 0 to 100. Higher scores indicate better functioning for the functioning scales and global QOL; for the symptom scales, higher scores indicate higher symptom burden (Aaronson et al., 1993).

Antidepressant Side-Effect Checklist (ASEC)

The Royal College of Psychiatrists developed ASEC to assess the 21 common adverse reactions to antidepressants, such as dry mouth, drowsiness, insomnia, and appetite. The severity of each item is rated on a 4-point scale (0 absent; 1 mild; 2 moderate; 3 severe), and it is specified whether the symptom, if present, was likely to be a side-effect of the antidepressant (yes or no)(Uher et al., 2012).

Data Collection

All eligible patients were briefed on the study protocol. Consenting patients were initiated on vortioxetine (Brintellix tablets) flexible dosing from 5mg to 10mg daily, at the discretion of their consulting psychiatrist. They were dispensed enough medication for self-administration to last until the following visit. A baseline measure for MADRS, CGI, PDQ-5, and EORTC QLQ-C30 was done. Patients were followed up either in person at the outpatient clinic or through scheduled phone calls at weeks 2, 4, 8, 12, 16, 20, and 24. The same measures were administered during the scheduled follow-ups along with the ASEC.

Sample Size Calculations

The sample size was calculated to detect at least a mean difference of 6.6 units in MADRS total score with a pooled standard deviation of 7.8 units (Baldwin et al., 2012) at 90% power and a 5% level of significance (two-sided). Hence 30 subjects were required for the study; however, accounting for a drop-out rate of 50%, 45 subjects were recruited.

Statistical Analysis

Statistical analyses were carried out using SPSS Statistics (IBM) version 25. Data analysis was based on the all-patients-treated set, i.e., all patients who took at least one vortioxetine dose. Descriptive statistics were used to summarise the patients' baseline demographic characteristics and the Treatment-Emergent Adverse Events (TEAE). Multiple imputations were carried out to account for missing data. The primary efficacy analysis was a repeated measures Analysis of Variance (ANOVA) of the change from baseline in total mean MADRS, CGI, PDQ-5, and EORTC QLQ-C30 scores at Weeks 2, 4, 8, 12, 16, 20, and 24. A graph was plotted to illustrate the changes in mean scores throughout the six months for MADRS and EORTC QLQ-C30. The primary outcome was changes in MADRS and PDQ-5 scores, while changes in EORTC QLQ-C30 and CGI were considered secondary outcomes. All statistical analyses were set at a significance level of $p<0.05$.

Results

Patient Baseline Characteristics

A total of 45 patients were included in the study; details of patients' allocation and follow-up are illustrated in Figure 1. Their baseline clinical and demographic characteristics are detailed in Table 1. The average age of the participants was around 53 years, with almost two-thirds females. More than half were Chinese (57.8%), 26.7% were Malay, and 6.7% were Indian. The mean baseline MADRS total score was 29.89 ± 5.997, indicating moderate to severe

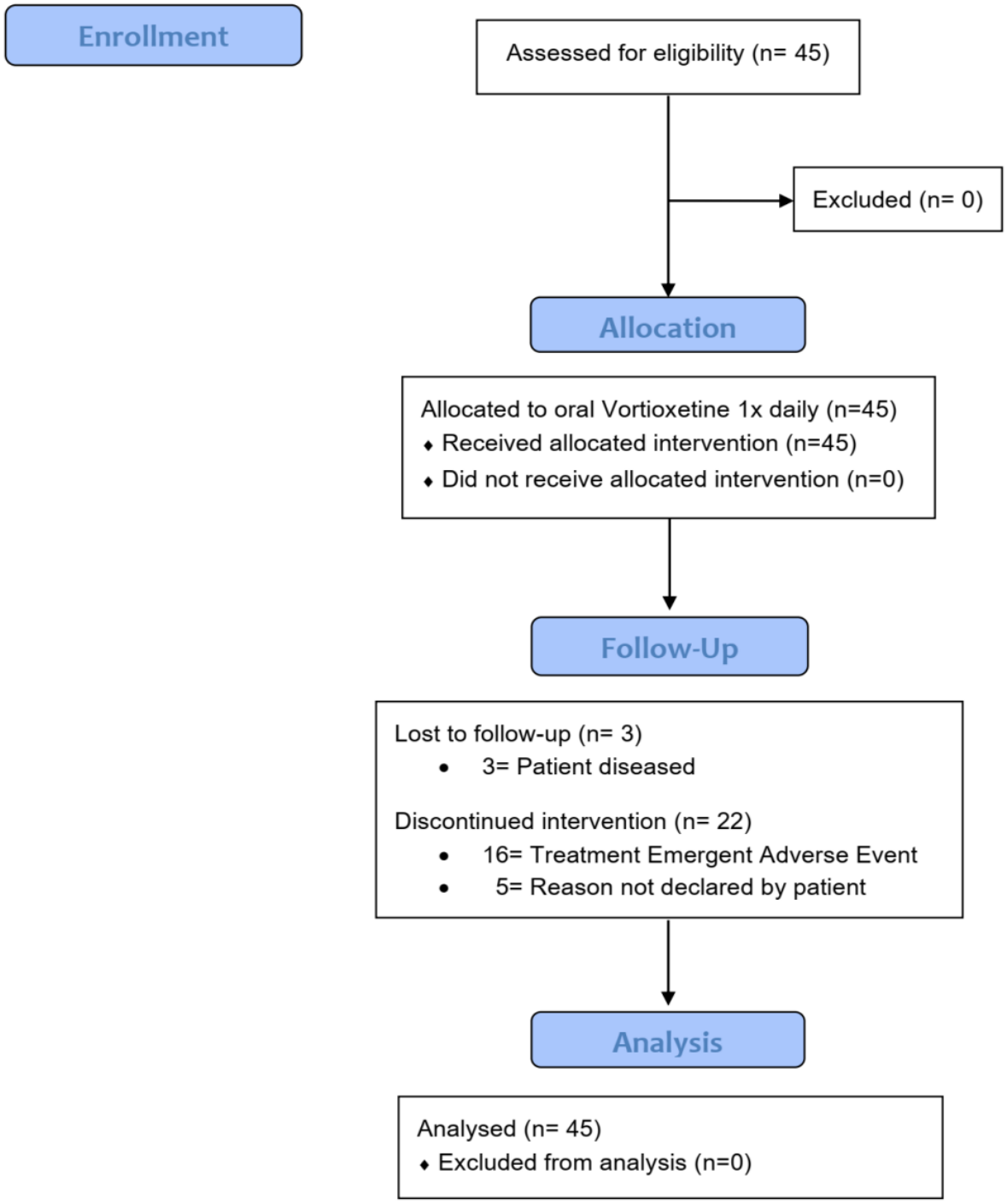

Figure 1. CONSORT Flow Diagram- Modified for Non-Randomized Trial Design

depression, consistent with the mean CGI-S score of 4.39 ± 0.746. The patients included in the study were diagnosed with a range of cancers, including breast cancer 46.7%, colon cancer 13.3%, endocrine cancer 2.2%, leukaemia 2.2%, liver cancer 4.4%, lymphoma 4.4%, ovarian cancer 2.2%, prostate cancer 6.7% and uterine cancer 4.4%. The vortioxetine dosing range was 5-20 mg daily.

Efficacy

Primary Efficacy Outcomes

Although there was variability in the patient dosing, data revealed (Table 2) a statistically significant difference in total MADRS from baseline starting from Week 2, this improvement in scores was maintained throughout the 24 weeks of the study. Patients experienced a reduction of 18 points in total MADRS scores from 29.89 ± 5.997 at baseline to 11.59 ± 4.629 by Week 24 (Figure 2). Furthermore, the PDQ-5 scores started to show significant change from baseline by Week-4; this significance in change was maintained for the rest of the study duration except for Week-8.

Secondary Efficacy Outcomes

Table 2 summarises the differences in scores of the secondary outcomes from baseline at Week 2 until Week 24; these include the CGI, EORTC quality of life, EORTC

Table 1. Baseline Patient Characteristics

Characteristics	Patients (n=45)
Gender n (%)	
Females	28 (62.2)
Males	14 (31.1)
Age (years)	
Mean ± SD	53.78 ± 13.06
Range	29.00 – 83.00
Ethnicity n (%)	
Chinese	26 (57.8)
Malay	12 (26.7)
Indian	3 (6.7)
Others	1 (2.2)
Type of cancer n (%)	
Breast cancer	21 (46.7)
Colon cancer	6 (13.3)
Endocrine cancer	1 (2.2)
Leukemia	1 (2.2)
Liver cancer	2 (4.4)
Lymphoma	2 (4.4)
Ovarian cancer	1 (2.2)
Prostate cancer	3 (6.7)
Uterine cancer	2 (4.4)
Rating scale scores	
MADRS total score	29.89 ± 5.997
CGI-S score	4.39 ± 0.746

physical functioning, EORTC role functioning, EORTC emotional functioning, EORTC social functioning, and EORTC cognitive functioning scores. Based on the repeated measures ANOVA, EORTC role functioning, EORTC emotional functioning, and EORTC cognitive functioning scores showed a significant change from baseline from Week 2 onwards, indicating an enhancement of the patients' quality of life. Furthermore, CGI-Severity scores decreased from a baseline of 4.39 ± 0.746 to 2.41 ± 1.085 by Week 24. The remaining scales start to show significant change starting from Week 4. However, the change in CGI-I was not significant except at Week 12; for the CGI-I the change for this scale was measured from Week 2, and no baseline scores were recorded.

Likewise, Figure 3 illustrates changes in the EORTC quality of life, EORTC physical functioning, EORTC role functioning, EORTC emotional functioning, EORTC social functioning, and EORTC cognitive functioning scores throughout the six months of therapy.There appears to be an overall increase in the EORTC scores from baseline as early as week 2, this increase has been sustained till week 16 despite the appararent fluctuation in scores across the study duration.

Tolerability and Safety

Adverse Events (AE)

During the 24 weeks of therapy with variable doses of vortioxetine, around three-quarters of the patients (73.3%)

Table 2. Mean Change from Baseline in Primary and Secondary Efficacy Outcomes (Repeated Measure ANOVA)

	Wk 2		Wk 4		Wk 8		Wk 12		Wk 16		Wk 20		Wk 24	
	Mean Difference	Std Error	Mean Difference	Std Error	Mean Difference	Std Error	Mean Difference	Std Error	Mean Difference	Std Error	Mean Difference	Std Error	Mean Difference	Std Error
Primary Efficacy Outcomes														
MADRS	7.585*	1.052	15.164*	1.002	15.534*	1.174	17.232*	1.147	17.182*	1.105	19.361*	1.127	18.318*	1.143
PDQ	1.883	0.614	3.076*	0.589	2.147	0.764	2.773*	0.672	2.997*	0.697	3.801*	0.726	3.364*	0.637
Secondary Efficacy Outcomes														
CGI-S	0.677*	0.144	1.371*	0.124	1.452*	0.134	1.652*	0.148	1.632*	0.148	1.995*	0.153	1.917*	0.16
CGI-I#	-	-	0.44	0.137	0.126	0.167	0.626*	0.147	0.146	0.153	0.394	0.15	0.216	0.149
EORTC QoL	-10.691	2.83	-16.758*	3.726	-14.580*	3.356	-17.629*	3.376	-22.090*	3.277	-24.026*	3.357	-21.049*	3.339
EORTC Physical Functioning	-8.671	3.232	-13.893*	4.08	-18.490*	4.748	-14.899	4.574	-11.899	4.645	-16.863*	4.31	-18.959*	4.141
EORTC Role Functioning	-21.327*	4.582	-31.981*	5.277	-26.474*	6.317	-22.547*	5.732	-25.213*	6.18	-28.233*	5.547	-29.242*	5.658
EORTC Emotional Functioning	-23.531*	4.285	-29.009*	4.248	-34.297*	4.193	-34.332*	4.201	-31.034*	4.149	-36.692*	4.1	-37.401*	4.087
EORTC Cognitive Functioning	-13.691*	3.919	-16.392*	4.276	-23.870*	4.41	-25.957*	3.998	-27.565*	4.308	-27.790*	4.51	-22.371*	4.034
EORTC Social Functioning	-9.648	4.908	-29.091*	5.466	-37.203*	6.053	-34.935*	5.722	-30.741*	5.381	-28.273*	5.434	-27.022*	5.27

MADRS, Montgomery-Asberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement; PDQ, Perceived Deficiency Questionnaire; EORTC, European Organization for Research and Treatment of Cancer; QoL, Quality of life; # Mean change from Weak 2 not baseline; * P-value <0.05

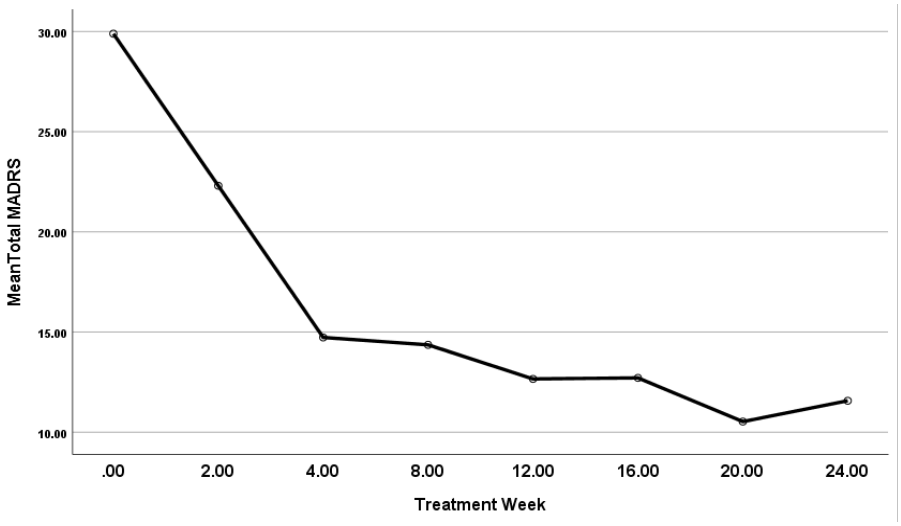

Figure 2. Mean Total Montgomery-Asberg Depression Rating Scale (MADRS) Score from Baseline to Week 24

had one or more adverse events. Out of the included 45 patients, 22 withdrew from the study, of which 16 patients (35.55 %) were due to Treatment-Emergent Adverse Events (TEAE). The most frequently reported TEAEs were dry mouth, insomnia, somnolence, and headache, with more than a 30% incidence rate. The frequency of TEAD reported by the patients is detailed in Table 3.

Serious Adverse Events (SAE)

Three deaths occurred during the study. The first was a 51-year-old woman with advanced rectosigmoid carcinoma involving lung and liver metastasis; the patient was in the study for around 20 Weeks. The second patient was a 70-year-old woman with intrahepatic cholangiocarcinoma; she died two weeks after inclusion in the study. The last case was a male, 80 years old with prostate carcinoma, who passed away two weeks following his entry to the trial. The investigator evaluated all the patients and assessed their death as a natural disease progression and not related to vortioxetine medication.

Discussion

Depressive symptoms are frequent among cancer patients, and their frequency has been well documented in the literature. However, given that depression is linked to poorer cancer outcomes, decreased patient quality of life, and non-compliance with chemotherapy, the coexistence of these two conditions can be particularly problematic. Accordingly, we conducted a study to assess the efficacy and tolerability of a novel multimodal antidepressant on cancer patients diagnosed with depression. To our knowledge, this is the first assessment of the effects of vortioxetine in this patient cohort. This research provides supporting evidence that vortioxetine has a positive impact on cancer patients' depressive symptoms,

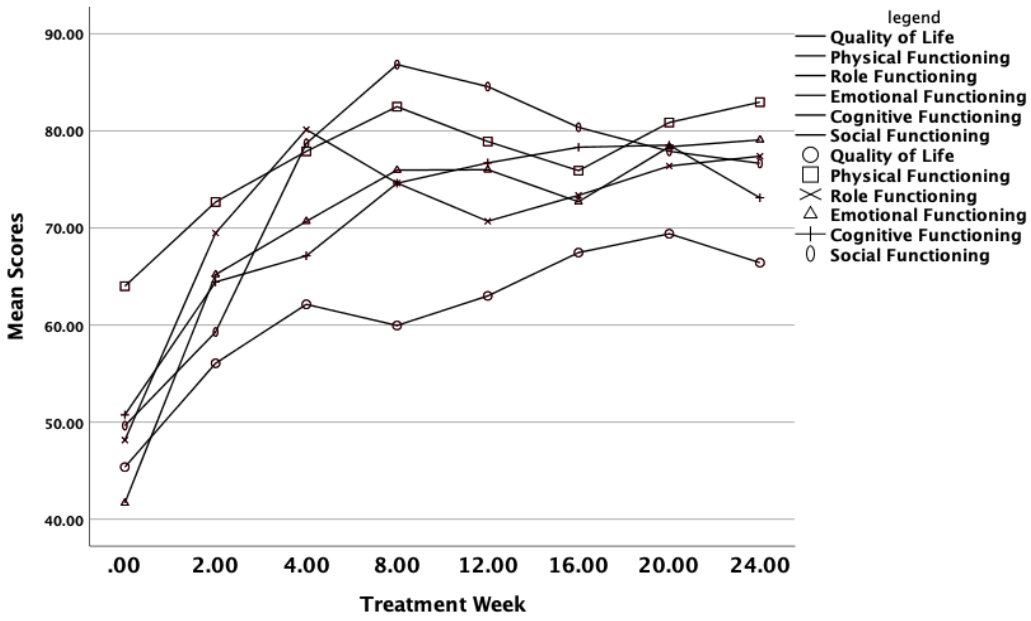

Figure 3. Mean Total European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) Scores from Baseline to Week 24

Table 3. Reported Incidence of Treatment-Emergent Adverse Events (TEAE) during the 24 Week Treatment Period

Adverse Event	N (%)
Patients with TEAE	33 (73.3%)
Dry mouth	46.70%
Insomnia	36.40%
Somnolence	35.70%
Headache	32.30%
Constipation	27.20%
Blurred vision	25.80%
Hyperhidrosis	23.40%
Palpitations	21.90%
Feeling light-headed on standing	21.40%
Yawning	20.20%
Decreased appetite	20.00%
Weight gain	19.80%
Nausea or Vomiting	19.40%
Feeling that the room is spinning	17.20%
Increased appetite	16.10%
Diarrhoea	15.90%
Increased body temperature	13.50%
Sexual dysfunction	11.80%
Tremor	10.90%
Disorientation	10.90%
Problems with urination	9.40%

cognitive function, and quality of life.

The findings of our study demonstrate a significant improvement in the mean total MADRS score as early as week 2; this change was maintained until week 24. This pattern of results is consistent with and extends the body of evidence on the positive impact of vortioxetine on adults with MDD previously reported (Alvarez et al., 2012; Boulenger et al., 2014). Both randomized, double-blinded placebo-controlled studies demonstrated a statistically significant change in MADRS total scores from baseline that is superior to placebo. Another key finding is the enhancement in the baseline patient-reported cognitive function scores set out from week four and maintained until week 8. Similar results were mirrored in a randomized, double-blind study on adults with recurrent MDD; the vortioxetine group showed significant improvement in objective and subjective cognitive function measures compared to the placebo (McIntyre et al., 2014). Furthermore, our results are highly consistent with the REVIDA study that demonstrated the efficacy of vortioxetine in reducing depressive symptoms and enhancing cognitive function among South-East Asian patients in clinical settings (Chin et al., 2018).

The enhancement in physician-reported CGI scales further supports the positive impact of vortioxetine on depression; both the improvement and severity scores showed significant change from baseline by week 24. The reduction in CGI scores is congruous with data from research and clinical settings related to vortioxetine use among adults with Major Depressive Disorder (Alvarez et al., 2012; Boulenger et al., 2012; Boulenger et al., 2014; Chin et al., 2018; McIntyre et al., 2014). The current study also highlighted the effect of vortioxetine on cancer patients' quality of life, which was assessed using the EORTC QLQ-C30 scale. The findings showed that the domains of role, emotional, and cognitive functioning improved significantly from Week 2. These results are corroborated by six short-term, placebo-controlled studies analyzed for the impact of vortioxetine on the health-related quality of life of adults with MDD (Florea et al., 2015). Vortioxetine demonstrated significantly better results than placebo in the vitality, social functioning, emotional role functioning, and mental health domains of the Short Form 36 Health Survey. Furthermore, it separated from the placebo on the European Quality of Life Scale and the Quality of Life Enjoyment and Satisfaction Questionnaire.

During the 24-week study period, around three-quarters of the patients reported one or more adverse events. Although this proportion is slightly higher than in past research, the medical history of our patient cohort provides a compelling explanation for these findings (Alvarez et al., 2012; Boulenger et al., 2014). In addition, side effects were actively assessed via the ASEC scale at all time points of this study. As such, this could induce a higher adverse event reporting than in real-life clinical practice, where patients spontaneously report adverse events. The most common adverse events during treatment, including dry mouth, insomnia, somnolence, and headache, are consistent with studies on treatment-related adverse events of vortioxetine (Alvarez et al., 2012; Boulenger et al., 2012; Boulenger et al., 2014). The withdrawal rate in this study is significantly higher than in other real-life studies of vortioxetine in Asia (Alvarez et al., 2012; Boulenger et al., 2012; Boulenger et al., 2014) and could be due to cancer exacerbating some of the adverse events.

This six-month open-label clinical trial was conducted to evaluate the efficacy and tolerability of vortioxetine in a small sample of cancer patients with depressive symptoms, however its findings are subject to several limitations. The first limitation concerns patient adherence; it was not possible for the investigators to confirm the reported patient adherence, especially since they were not required to stay on-site throughout the study duration. Another potential limitation, notwithstanding the positive study results, is the small sample size and the absence of a placebo/comparator arm rendering the findings exploratory in nature. Additionally, the use of questionnaires that have not been validated within the population of interest exposed the data to potential measurement error, thereby the results are to be interpreted with caution. Another major source of uncertainity is the impact of confounding variables, this study had no restrictions on concomitant psychotherapy, and hence its effect on the research outcomes cannot be ruled out. Furthermore, almost half of the subjects enrolled in the study were breast cancer patients, thereby affecting the potential pertinency of its findings to other types of cancers, including advanced or palliative cases. These limitations affect the potential

generalizability of the study findings beyond the clinical trial setting and suggest the need for future research to evaluate the effect of vortioxetine on depression, cognitive function, and quality of life of depressed cancer patients.

The current study fills the gap in research on the effect of multimodal antidepressants on cancer patients with depression. Despite its limitations, the results suggest that vortioxetine is efficacious in reducing depressive symptoms and enhancing this patient cohort's cognitive function and quality of life. Future randomized controlled clinical trials evaluating the efficacy and safety of vortioxetine in larger cancer populations are warranted.

In conclusions, the present study supports the growing body of evidence on the efficacy of vortioxetine, 5–20 mg/day, in the management of depression, enhancement of cognitive function, and quality of life of cancer patients with Major Depressive Disorder. Findings from this research suggest that vortioxetine at the earlier mentioned doses can be utilized in future clinical trials to evaluate its comparative efficacy among cancer patients with depression.

Author Contribution Statement

Conception and design: NCG, AAA, LSY; Methodology: NCG, AAA, LSY, NZZ; Data collection, formal analysis and investigation: NCG, AAA, LSY, NZZ, TKS, ABA, LTH, SBY, NRNJ, NIBAT, NABMK, FI, WZW; Writing - original draft preparation: AAA, LSY; Writing - review and editing: NCG, AAA, LSY; Supervision: NCG, AAA. All authors read and approved the final manuscript.

Acknowledgements

We acknowledge the following hospitals for their invaluable support and contribution to the study University of Malaya Medical Centre, Hospital Putrajaya, Hospital Raja Permaisuri Bainun, Hospital Kuala Lumpur, and Universiti Kebangsaan Malaysia Medical Centre.

Funding

This study was an investigator-initiated trial with grant support from Lundbeck South East Asia.

Ethical approval

The study procedures were approved by the Medical Research Ethics Committee (MREC), University of Malaya Medical Centre (UMMC) [MRECID.NO: 201972-7593], and Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia [NMMR-19-2850-50323].

Clinical trial registration

The trial protocol was registered at ClinicalTrials.gov (NCT04253678)

Conflict of interest

The authors have no conflicts of interest to declare.

References

Aaronson NK, Ahmedzai S, Bergman B, et al (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, **85**, 365-76.

Alvarez E, Perez V, Dragheim M, et al (2012). A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*, **15**, 589-600.

Asberg M, Montgomery SA, Perris C, et al (1978). A comprehensive psychopathological rating scale. *Acta Psychiatr Scand Suppl*, **271**, 5-27.

Baldwin DS, Hansen T, Florea I (2012). Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin*, **28**, 1717-24.

Bennabi D, Haffen E, Van Waes V (2019). Vortioxetine for Cognitive Enhancement in Major Depression: From Animal Models to Clinical Research. *Front Psychiatry*, **10**, 771.

Boulenger JP, Loft H, Florea I (2012). A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *J Psychopharmacol*, **26**, 1408-16.

Boulenger JP, Loft H, Olsen CK (2014). Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol*, **29**, 138-49.

Chin CN, Zain A, Hemrungrojn S, et al (2018). Results of a real-world study on vortioxetine in patients with major depressive disorder in South East Asia (REVIDA). *Curr Med Res Opin*, **34**, 1975-84.

Chochinov HM (2001). Depression in cancer patients. *Lancet Oncol*, **2**, 499-505.

Connolly KR, Thase ME (2016). Vortioxetine: a new treatment for major depressive disorder. *Exp Opin Pharmacother*, **17**, 421-31.

D'agostino A, English CD, Rey JA (2015). Vortioxetine (brintellix): a new serotonergic antidepressant. *Pharm Therap*, **40**, 36.

Di Iulio F, Cravello L, Shofany J, et al (2019). Neuropsychological disorders in non-central nervous system cancer: a review of objective cognitive impairment, depression, and related rehabilitation options. *Neurol Sci*, **40**, 1759-74.

Doan L, Manders T, Wang J (2015). Neuroplasticity underlying the comorbidity of pain and depression. *Neural Plast*, **2015**, 504691.

Fann JR, Thomas-Rich AM, Katon WJ, et al (2008). Major depression after breast cancer: a review of epidemiology and treatment. *Gen Hosp Psychiatry*, **30**, 112-26.

Florea I, Danchenko N, Brignone M, et al (2015). The effect of vortioxetine on health-related quality of life in patients with major depressive disorder. *Clin Ther*, **37**, 2309-23.

Friedrich MJ (2017). Depression Is the Leading Cause of Disability Around the World. *JAMA*, **317**, 1517.

Guy W (1976). ECDEU assessment manual for psychopharmacology Revised. Clinical Global Impressions. US Department of Health, Education, and Welfare Publication (ADM), Rockville Maryland, pp 217-22.

Hemeryck A, Belpaire FM (2002). Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab*, **3**, 13-37.

Hybels CF, Pieper CF, Payne ME, Steffens DC (2016). Late-life depression modifies the association between cerebral white matter hyperintensities and functional decline among older

adults. *Am J Geriatr Psychiatry*, **24**, 42-9.
Katona C, Hansen T, Olsen CK (2012). A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*, **27**, 215-23.
Lam RW, Lamy FX, Danchenko N, et al (2018). Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. *Neuropsychiatr Dis Treat*, **14**, 2861-77.
Levada OA, Troyan AS (2019). Cognitive-functional relationships in major depressive disorder: Crucial data from a Ukrainian open-label study of vortioxetine versus escitalopram. *J Affect Disord Actions*, **250**, 114-22.
Lin JH, Huang MW, Wang DW, et al (2014). Late-life depression and quality of life in a geriatric evaluation and management unit: an exploratory study. *BMC Geriatrics*, **14**, 1-7.
Lundbeck. (2018). FDA updates Trintellix® (vortioxetine) label to include data showing improvement in processing speed, an important aspect of cognitive function in acute Major Depressive Disorder (MDD). GlobalNewsWire.
Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS (2015). A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology*, **40**, 2025-37.
McIntyre RS, Lophaven S, Olsen CK (2014). A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*, **17**, 1557-67.
Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry*, **134**, 382-9.
Niedzwiedz CL, Knifton L, Robb KA, Katikireddi SV, Smith DJ (2019). Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. *BMC Cancer*, **19**, 943.
Nomikos GG, Tomori D, Zhong W, Affinito J, Palo W (2017). Efficacy, safety, and tolerability of vortioxetine for the treatment of major depressive disorder in patients aged 55 years or older. *CNS Spectrums*, **22**, 348-62.
Sanchez C, Asin KE, Artigas F (2015). Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther*, **145**, 43-57.
Smith J, Browning M, Conen S, et al (2018). Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. *Mol Psychiatry*, **23**, 1127-33.
Sotelo JL, Musselman D, Nemeroff C (2014). The biology of depression in cancer and the relationship between depression and cancer progression. *Int Rev Psychiatry*, **26**, 16-30.
Spina E, Santoro V (2015). Drug interactions with vortioxetine, a new multimodal antidepressant. *Riv Psichiatr*, **50**, 210-15.
Uher R, Perlis RH, Henigsberg N, et al (2012). Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychol Med*, **42**, 967-80.