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Pharmacogenetics of escitalopram and mental adaptation to cancer in palliative care: report of 18 cases

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ABSTRACT

Aims and background. In palliative care, few data are available on the diagnosis and treatment of mood disorders and of difficulties of mental adaptation to cancer for patients in the advanced phases of the disease. SSRI antidepressants are the treatment of choice; the 5-HTTLPR genetic polymorphism of the serotonin transporter (SERT) has been shown in psychiatry to significantly determine the therapeutic response and the incidence of adverse effects. The aim of the present investigation has been therefore to examine the effects of the SSRI antidepressant escitalopram, also considering 5-HTTLPR, on depression, anxiety and mental adaptation to cancer in palliative care.

Methods and study design. Eighteen consecutive depressed patients with different forms of advanced cancer admitted to the Hospice Ass 6 of S. Vito al Tagliamento (Pordenone, Italy) were genotyped for the "s" and "l" variants of 5-HTTLPR and were treated with escitalopram. Their response after two weeks of treatment was psychometrically evaluated.

Results. Treatment with escitalopram significantly decreased anxiety scores on the Hospital Anxiety and Depression Scale (HADS) ($P = 0.006$) as well as anxious preoccupation ($P = 0.007$) and hopelessness-helplessness ($P = 0.017$) scores on the Mini Mental Adjustment to Cancer (Mini-MAC) scale. When patients were stratified by SERT genotype, HADS anxiety was significantly decreased in patients carrying the "s/s" and "s/l" variants ($P = 0.024$), whereas those with an "l/l" genotype displayed a significant reduction of Mini-MAC anxious preoccupation ($P = 0.018$).

Conclusions. The results of this study indicate that the use of SSRI antidepressants is effective in the palliative care of cancer patients, and their action affects not only depression but also the patients' mental adaptation to the disease. These results encourage further examination of these drugs in a larger cohort of patients. The significant contribution of pharmacogenetics indicates the possibility of personalized treatment with SSRIs in palliative care.

Key words: palliative care, pharmacogenetics, antidepressant drugs, mental adaptation to cancer.

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Introduction

Depressive mood disorders show a growing incidence and prevalence in the general population, and are correspondingly identified with increasing frequency in cancer patients[1,2]. In these patients, depression is related to several dimensions of abnormal illness behavior (e.g., hypochondriasis, irritability, denial)[3] and is also associated with reduced quality of life, pain, and suicidal risk[4].

In addition to depression, and excluding pre-existing or latent psychiatric disorders, psychological difficulties in cancer patients may consist of complex features requiring diagnostic criteria differing from classic psychopathological categorization.

Specific psychometric instruments have been developed and employed for depression and anxiety (Hospital Anxiety and Depression Scale, HADS)[5] and mental adaptation to cancer (Mental Adjustment to Cancer Scale, Mini-MAC)[6]. The literature on mood disorders and difficulties of mental adaptation to the disease in patients with advanced cancer appears limited[7-9].

When depression is treated with drugs, SSRI antidepressants are the most frequently used agents[10-14]. The effects of the treatment with SSRIs has been shown to depend on pharmacogenetics, in particular on the polymorphism of the gene coding for the serotonin transporter (SERT, 5-HTT)[15-20], which is the molecular target of SSRI's action. 5-HTTLPR (5-hydroxytryptamine transporter-gene-linked polymorphic region) is a polymorphism occurring in the promoter region of the SERT gene and consists of insertion/deletion of 44 base pairs, resulting in a long ("l") or short ("s") allele causing high ("l/l") or low ("s/s", "s/l") functional activity, respectively[21]. The different activity of the transporter thus determines the response to the SSRIs. Indeed, most available studies suggest that homozygotes for the "l/l" variant of 5-HTT respond faster and better to SSRI treatment than carriers of the "s/s" and "s/l" variants[15,16]. Conversely, the presence of the "s/s" and "s/l" alleles was strongly associated with the incidence of adverse effects[17,18].

In palliative care, preliminary investigations have shown that treatment with sertraline and citalopram reduced depression and anxiety as determined by HADS. Sertraline also facilitated mental adaptation to cancer as measured with Mini-MAC. The action of both drugs on depression and mental adaptation to cancer depended on the 5-HTTLPR polymorphism[12,13].

The aim of the present investigation was therefore to examine the effects of the SSRI antidepressant escitalopram in palliative care. We assessed the effects of the drug on depression, anxiety and mental adaptation to cancer in patients with various types of advanced cancer. The results were analyzed also in relation to the genetic polymorphism of the serotonin transporter.

Materials and methods

Patients

The subjects initially included in this study were 46 consecutive patients, 25 men (54%) and 21 women (46%), who were admitted to the hospice of the Azienda per i Servizi Sanitari 6, S. Vito al Tagliamento (Pordenone, Italy). All patients had a diagnosis of cancer and their tumors were located in the breast (5 patients), ovary (2 patients), brain (2 patients), kidney (2 patients), colon (2 patients), prostate (2 patients), lung (2 patients), and tongue (1 patient); one tumor had an unreported origin (1 patient) [AUTHORS: These figures do not add up to 46. Do they refer only to the actual study group mentioned later? Then this should be stated.]. Eleven patients (61%) were treated with chemotherapy, 5 (27%) with radiotherapy, and 9 (50%) with surgery; 15 patients (83%) had metastases. The majority of the patients (94%) had a Karnofsky performance score ranging between 40 and 60.

Each patient was carefully evaluated at admission by the palliative care team, and those who met the criteria for a depressive disorder according to DSM-IV and who were clinically judged to potentially benefit from antidepressant treatment were treated with escitalopram. Eighteen patients (10 men and 8 women) completed a period of 2 weeks' treatment, and their characteristics are reported in the study.

The patients received detailed information about the procedure of the present study and expressed their written informed consent to participate in the investigation. The study protocol was prepared in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and received a positive review by the pertinent ethics committee. For each patient, the demographic as well as the previous and current medical history were recorded anonymously for later analysis.

Treatments and psychometry

All study participants were psychometrically evaluated for depression and anxiety by a trained psychologist using HADS[18], and for their mental adaptation to cancer using the Mini-MAC[19]. The psychometric scales were administered at admission to the hospice and recruitment to the study (T0), and after 14 days (T1) of daily treatment with 10 mg escitalopram per os.

Polymorphism analysis

The patients were genotyped for 5-HTTLPR polymorphism by analysis of genomic DNA obtained from buccal mucosa cells with standard procedures (MasterAmp™ buccal swab brushes, Epicentre Biotechnologies; GenElute™ Blood genomic DNA kit, Sigma). Polymerase chain reaction (PCR) and electrophoretic analysis were performed using conventional techniques that have been described in detail elsewhere[12-14].

Statistical analysis

The scores of the psychometric measures obtained at admission (T0) and at the end of treatment (T1) were analyzed in relation to the genotypes of the patients using nonparametric techniques (Kruskal-Wallis, Mann-Whitney and Wilcoxon tests), as well as chi-square analysis for multiway frequency tables. Statistical analysis was done with the standard software package SYSTAT 10 (Systat Software Inc., San Jose, CA, USA). Statistical significance was set at the $P < 0.05$ level.

Results

Analysis of the scores of the psychometric assessment at admission revealed that there were no significant differences between patients who completed 2 weeks' treatment with escitalopram and those who dropped out earlier and were not included in the study, for any of the variables considered (sex, previous treatment, tumor stage, Karnofsky status, opioid use, HADS and Mini-MAC scores, and genotype polymorphisms; Fisher's exact test and Kruskal-Wallis test).

The patients enrolled in this study, in addition to escitalopram were also treated with one or more of the following drugs: 11 patients (61%) received non-opioid analgesics for pain, 13 (72%) opioids, 14 (77%) benzodiazepines and 2 (11%) received antipsychotics. The psychometric scores of the patients considered in the study were not significantly influenced by any of these drug treatments (Fisher's exact test and Kruskal-Wallis test). In patients who were treated with radiotherapy, significantly higher scores of hopelessness-helplessness and lower scores of fatalism were observed (Kruskal-Wallis test).

After 2 weeks of treatment with escitalopram, a significant reduction was observed in anxiety scores on HADS and in anxious preoccupation and hopelessness-helplessness scores on the Mini-MAC (Table 1). Of the 18 patients considered, 11 (61%) were found to carry at least one "s" allele (2 "s/s" and 9 "s/l" variants), and 7 (39%) were homozygous for the "l/l" alleles. When the 5-HTTLPR polymorphism was considered, HADS anxiety scores were significantly decreased only in patients carrying the "s/s" and "s/l" variants, whereas those with "l/l" genotypes displayed a significant reduction of Mini-MAC anxious preoccupation (Table 2); no significant difference was found for the remaining subscales.

Discussion

Depressive mood disorders show an increasing incidence and prevalence in the general population and are extensively treated with antidepressants, in particular SSRIs. Difficulties in the mental adaptation to cancer are common in patients with advanced disease and may significantly and negatively affect quality of life; yet, studies on the effects of treatment with SSRI antidepressants in these patients are scarce.

In the present study, treatment with escitalopram significantly attenuated anxiety as identified using HADS and improved the mental adaptation to cancer by reducing anxious preoccupation and hopelessness-helplessness as determined with Mini-MAC. Concomitant palliative treatments received did not significantly influence the mental status of the patients or their response to escitalopram. It is noteworthy that those patients who received radiotherapy before recruitment later had higher scores of hopelessness-helplessness and lower scores of fatalism; this did not affect the results presented but seems to deserve attention, which may be the scope of a further study.

The results of this study also indicate that the effects of escitalopram on anxiety and anxious preoccupation depended on 5-HTTLPR genetic polymorphism. In fact, anxiety was significantly and markedly reduced only in carriers of at least one "s" allele, whereas a significant and marked reduction of anxious preoccupation occurred only in homozygotes for the "l" allele.

When the responses to citalopram and sertraline were previously examined in the same palliative care setting, significant effects were reported[12,13]. Citalopram was found to attenuate, in addiction to anxiety, also depression in a genotype-dependent way[13]. Sertraline, on the other hand, displayed a wider spectrum of action extended to most of the psychometric variables considered[12].

The characterization of the patients' genetic polymorphism of the serotonin transporter 5-HTTLPR thus appears to contribute significantly to the therapeutic response to SSRIs, indicating that pharmacogenetics can be usefully integrated in the palliative care for the treatment of mood disorders and difficulties in the mental adaptation to cancer in patients with advanced disease.

Table 1 - Effects of treatment with escitalopram

		N	Treatment (days)	Average score ± SD[#]	*P**
HADS	Anxiety	18	0	8.2 ± 3.8	0.006
			14	5.9 ± 3.9	
Mini-MAC	Anxious preoccupation	18	0	19.3 ± 3.9	0.007
			14	16.3 ± 4.0	
	Hopelessness-helplessness	18	0	22.8 ± 3.9	0.017
			14	20.3 ± 5.0	

[#] The scores reported are the mean ± SD and the median of the subscale reported at admission and after 14 days of treatment.
* Probability, Wilcoxon test.

Table 2 - Response to treatment with escitalopram and SERT genotype

		Allelic variant (functionality)	N	Treatment (days)	Average score ± SD[#]	*P**
HADS	Anxiety	s/s, s/l (low)	11	0	7.8 ± 4.1	0.024
				14	5.7 ± 3.8	
		l/l (high)	7	0	8.8 ± 2.7	0.128
				14	6.3 ± 3.8	
Mini-MAC	Anxious preoccupation	s/s, s/l (low)	11	0	18.3 ± 4.2	0.094
				14	16.0 ± 5.2	
		l/l (high)	7	0	21.0 ± 3.1	0.018
				14	16.7 ± 1.6	

[#] The scores reported are the mean ± SD and the median of the subscale reported at admission and after 14 days of treatment.
* Probability, Wilcoxon test

The number of cases which could be recruited so far in the hospice for cancer palliative care is limited. However, the results obtained encourage further examination in palliative care settings of a larger cohort of patients, in order to validate the results presented and elucidate the properties of SSRIs, including examination of the role played by additional pharmacogenetic variables such as polymorphisms of CYP2D6 or CYP2C19 [22,23] and of the drug transporter gene ABCB1[24].

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