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Serotonin transporter 5-HTTLPR polymorphism and response to citalopram in terminally ill cancer patients: report of twenty-one cases

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ABSTRACT

The aim of this study was to examine the effects of the SSRI antidepressant drug citalopram on anxiety, depression and mental adjustment to cancer in terminally ill cancer patients, considering also the 5-HTTLPR genetic polymorphism.

A group of twenty-one consecutive patients admitted to the hospice of the *Casa di Cura Pineta del Carso* (Trieste, Italy) with different types of advanced cancer, who were clinically judged to require treatment with an antidepressive drug, was treated with citalopram for two weeks. The response was determined and related to 5-HTTLPR.

Citalopram significantly reduced the scores on the depression and anxiety subscales of the Hospital Anxiety and Depression Scale (HADS). When the effects of citalopram were analyzed in relation to the 5-HTTLPR polymorphism, the HADS depression score was significantly decreased only in patients with the "l/l" allelic variant of the serotonin transporter conferring high functional activity, while the score of the Mini-MAC fatalism scale was significantly increased in patients carrying at least one "s" allele.

These preliminary findings seem to indicate that two weeks of treatment with citalopram are effective in reducing depressive symptoms in terminally ill cancer patients. Moreover, the effects of citalopram on fatalism as a strategy of mental adaptation to cancer, and on depressive symptoms depend on the allelic variants of the 5-HTTLPR genotype of the patients. These results seem to encourage the examination of a larger patient sample and of different treatment schedules, as well as a more thorough characterization of fatalism as a coping strategy in cancer patients.

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

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Introduction

Depression is highly prevalent and difficult to assess in terminally ill cancer patients[1,2]. As a result, depression is frequently underdiagnosed and undertreated[3,4], with negative consequences for the patients' quality of life[5,6]. The identification and treatment of patients suffering from depression thus appears important in order to provide clinicians with an opportunity to relieve patients' suffering in palliative care[6]. Pharmacotherapy (antidepressants, anxiolytics and antipsychotics) is often effective in allaying distress in the terminal stage of illness[7], and has been shown also to improve coping skills and quality of life[8]. However, although SSRIs are currently the treatment of choice for depression[9-11], the response to antidepressants shows remarkable heterogeneity, which has been attributed to a variety of possible causes including the genetic polymorphism of the gene coding for the serotonin transporter 5-HTT[12,13]. 5-HTTLPR (5-hydroxytryptamine transporter-gene-linked polymorphic region) is a polymorphism which occurs in the promoter region of the 5-HTT gene and consists of insertion/deletion of 44 bp, resulting in a long ("l") or short ("s") allele[14].

The results of the majority of the available studies suggest that carriers of the "l/l and "l/s" allelic variants of 5-HTT show a better and faster response to SSRIs than "s/s" homozygotes[15-17]. Conversely, the presence of the low-expression "s/s" and "s/l" alleles was the strongest risk factor associated with adverse effect burden[18,19].

The aim of this study was therefore to examine the efficacy of the SSRI citalopram in a series of depressed terminally ill cancer patients admitted to the hospice of the *Casa di Cura Pineta del Carso* and to determine the relation of the 5-HTTLPR polymorphism to the patients' response to this drug. The effects of the drug were evaluated in terms of depression and anxiety as well as mental adaptation to cancer.

Patients and methods

Patients

The study subjects were 50 consecutive patients, 26 men (52%) and 24 women (48%), with advanced cancer admitted to the hospice of the *Casa di Cura Pineta del Carso* (Trieste, Italy). All patients were carefully evaluated at admission by the palliative care team, and those who met the criteria for a depressive disorder according to DSM-IV and were clinically judged to potentially benefit from antidepressive treatment were treated daily with 20 mg oral citalopram. The 21 patients included in the study stayed at the hospice and received the antidepressant treatment for at least 2 weeks. The study protocol was drawn up in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and received a positive review from the pertinent ethics committee. All patients received detailed information about the study and gave their written consent for participation. For each patient, demographic data as well as previous and current medical history were recorded.

Treatment and psychometry

Psychological assessment was carried out by a trained psychologist using the Hospital Anxiety and Depression Scale (HADS)[20,21] and the Mini-Mental Adjustment to Cancer Scale (Mini-MAC)[22,23]. HADS is a 14-item questionnaire measuring anxiety (7 items) and depression (7 items), and is designed for use in medical outpatients; the Mini-MAC is a 29-item questionnaire measuring patients' coping with cancer (fighting spirit, avoidance, hopelessness, anxious preoccupation and fatalism). Both scales were administered at recruitment (T0) and after 2 weeks of treatment (T1).

Polymorphism analysis

The patients were also genotyped for the polymorphism in the 5-HTT promoter region (5-HTTLPR) by analyzing genomic DNA obtained from whole blood or buccal cells using standard procedures (MasterAmp™ buccal swab brushes, Epicentre Technologies; GenElute™ blood Genomic DNA Kit, Sigma). Polymerase chain reaction (PCR) amplification of 5-HTTLPR was performed using the primers described by Gelernter[24], and with the GC-rich PCR System (Roche Molecular Biomedicals) in a 50-µL reaction containing 20-100 ng of DNA, 100 µm deoxyribonucleoside triphosphate (dNTPs), 20 pmol for each primer, and 1.5 mM $MgCl_2$. DNA was denatured at 95°C for 10 minutes and subjected to 40 cycles of 40 seconds of denaturation at 94°C, 45 seconds of annealing at 56°C, 40 seconds of extension at 72°C, and 10 minutes of final extension at 72°C. The PCR amplification products were separated on a 2% agarose gel and visualized in ultraviolet light after ethidium bromide staining.

Statistical analysis

The scores of the psychometric scales obtained at admission (T0) and after 2 weeks of treatment (T1), and their differences also in relation to the genotype of the patients were analyzed using nonparametric tests. Standard techniques including the Kruskal-Wallis, Mann-Whitney and Wilcoxon tests, as well as chi-square analysis for multiway frequency tables, were employed using the standard software package Systat 10 (Systat Software Inc., San Jose, CA, USA).

Results

Fifty patients were initially selected (T0) to receive treatment with citalopram; during the 2-week period of treatment, 6 patients were discharged and 23 died. Twenty-one of the patients initially recruited could thus be retested at T1 after 2 weeks of treatment and made up the group whose analysis is reported in this study. Ten patients were men (48%) and 11 women (52%), with a mean age of 71.1±12.1 years (range, 54-95 years). The tumors of the patients were located in the colon/rectum (4 patients), pancreas (3 patients), lung (2 patients), prostate (2 patients), breast (2 patients), liver (2 patients), esophagus (2 patients) and brain, stomach, ethmoid bone and hematological system in 1 patient each. Eleven patients (52%) had been treated with chemotherapy, 6 (28%) with radiotherapy, and 13 (62%) with surgery; 16 patients (80%) had metastases. The patients were treated with 1 or more drugs; 14 patients (66%) received non-opioid analgesics for pain, 17 (80%) opioids, 16 (80%) benzodiazepines, and 5 (20%) antipsychotics. The majority of the patients (64%) had a Karnofsky performance score of 40-60.

No significant differences at admission were found between the patients who dropped out and those who completed the treatment in any of the variables considered such as sex, previous treatment, tumor stage,

Karnofsky index, drug treatment, HADS and Mini-MAC scores, and genotype polymorphism (Fisher's exact test of distribution and Kruskal-Wallis test). Treatment for 2 weeks with psychotropic and analgesic drugs did not cause any statistically significant effect on the HADS and Mini-MAC scores.

Of the 21 patients retested at T1, 10 (48%) were carriers of a variant with one "s" allele (2 "s/s" and 8 "s/l" variants) and 11 were homozygous for the "l/l" allele (52%). No association was found between the scores of the psychometric scales and the clinical and demographic variables (sex, histology and stage of the tumor, Karnofsky score) determined at enrolment and the patient's 5-HTTLPR genotype.

The effects of citalopram treatment at T1 were significant and amounted to a reduction of the scores of both the anxiety and depression subscales of HADS ($P<0.05$), whereas no difference was found on any of the Mini-MAC subscales (Table 1). When the effects of citalopram were analyzed at T1 in relation to the 5-HTTLPR polymorphism, the scores of the HADS depression scale were significantly lower only in the patients with the "l/l" allelic variant of 5-HTT, whereas the Mini-MAC fatalism score was significantly increased in patients carrying the "s/s" and "s/l" allelic variants (Table 2). No significant difference was found for the remaining subscales.

Discussion

The data presented here suggest that citalopram is effective in reducing depression in terminally ill cancer patients after 2 weeks of treatment, and that anxiety was also significantly attenuated in these patients; no appreciable effect on the patients' coping with cancer repertoire was found. These findings are consistent with those reported by Theobald *et al.*[25] regarding the efficacy of citalopram in ambulatory cancer patients in the specific clinical context of the advanced phases of cancer.

Considering the molecular genetic characterization of 5-HTTLPR, approximately the same proportion of the patients considered had the "l/l" (11/21) and the "s/s" or "s/l" (10/21) allelic variants, endowed with high or low functional activity of 5-HTT, respectively[14]. When the effects of citalopram were analyzed according to 5-HTTLPR genotype characterization, drug treatment significantly reduced the HADS depression score only in patients carrying the highly functional genotypic variant "l/l", while it increased the score on the Mini-MAC fatalism subscale in patients carrying the "s/s" or "s/l" low-functionality variants.

The results of this study are consistent with the preliminary results obtained by the authors in palliative care, which showed that the effects of the SSRI sertraline were dependent on the 5-HTTLPR polymorphism[26].

Table 1 - Effects of citalopram on HADS anxiety and depression

	N	Time (days[$])	Average score (± SE)	Median (quartiles)	P[#]
HADS Depression	21	0 14	9.8 ± 1.3 7.8 ± 1.1	8.0 (5.0 - 16.0) 7.0 (4.5 - 9.5)	0.047
HADS Anxiety	21	0 14	5.5 ± 1.2 4.3 ± 1.1	4.0 (0.5 - 10.0) 3.0 (0.0 - 6.5)	0.047

HADS, Hospital Anxiety and Depression Scale. [$]The scores reported are those at admission (T0) and at retest 14 days later (T1). [#]Probability, Wilcoxon test.

Table 2 - Response to treatment with citalopram and SERT genotype

	Allelic variant (functionality)	N	Time (days[$])	Average score ± SE	Median (quartiles)	P[#]
HADS Depression	s/s, s/l (low)	10	0 14	7.4 ± 1.7 6.6 ± 1.3	6.0 (3.8 - 9.7) 6.0 (4.3 - 8.3)	0.634
	l/l (high)	11	0 14	12.1 ± 1.6 8.8 ± 1.8	12.0 (8.0 - 18.0) 9.0 (4.0 - 14.0)	0.030
Mini-MAC Fatalism	s/s, s/l (low)	10	0 14	10.8 ± 0.4 12.1 ± 0.5	11.0 (9.8 - 11.3) 12.0 (10.8 -13.0)	0.020
	l/l (high)	11	0 14	12.0 ± 0.3 11.2 ± 0.3	12.0 (11.0 -13.0) 11.0 (11.0 -12.0)	0.121

HADS, Hospital Anxiety and Depression Scale. [#]Probability, Wilcoxon test. [$]The scores reported are those at admission (T0) and at retest 14 days later (T1).

Moreover, these results are in general agreement with the pharmacogenetics of citalopram as a drug endowed with antidepressant, as well as anxiolytic, properties[27], and indicate that citalopram exerts a significant therapeutic action not only in depressed patients without concomitant somatic illness but also in terminally ill cancer patients. Moreover, in agreement with the available evidence, they show better antidepressant outcomes in patients carrying the "l/l" variant of 5-HTTLPR, although Kim *et al.*, in a study carried out in Korea, found that the favorable allele for SSRI response in white patients was the "s" form of 5-HTTLPR[28] . The observed increase in fatalism by citalopram in patients carrying the "s" allele is interesting, also considering that Cordova reported in a sample of nonterminally ill patients with cancer at various stages that fatalism, as identified by the Mini-MAC, was unrelated to a mood disturbance[29]. However, a detailed investigation into fatalism in relation to its value for the style of coping with the final stage of the disease and to mood disturbance in a larger patient population seems to be needed.

In spite of the limited number of patients in this study, these preliminary findings suggest that treatment with an SSRI antidepressant in palliative care may be effective against depression, as well as anxiety, after at least 2 weeks. Moreover, they indicate that the response to treatment in terms of depression and of fatalism as a strategy of adaptation to the disease significantly depends on the pharmacogenetic characteristics of the patients, thus encouraging a more thorough examination of a larger sample of patients, which is currently being performed.

References

1. Irwin SA, Rao S, Bower K, Palica J, Rao SS, Maglione JE, Soskin M, Betterton AE, Ferris FD: Psychiatric issues in palliative care: recognition of depression in patients enrolled in hospice care. J Palliat Med, 11: 158-163, 2008.
2. Akechi T, Okuyama T, Sugawara Y, Nakano T, Shima Y, Uchitomi Y: Major depression, adjustment disorders, and post-traumatic stress disorders in terminally ill cancer patients: associated and predictive factors. J Clin Oncol, 22: 1957-1965, 2004.
3. Lloyd-Williams M: Difficulties in diagnosing and treating depression in the terminally ill cancer patient. Postgrad Med J, 76: 555-558, 2000.
4. Miller KE, Adams SM, Miller MM: Antidepressant medication use in palliative care. Am J Hosp Palliat Care, 23: 127-133, 2006.
5. Chochinov HM: Dying, Dignity, and new horizons in palliative end-of-life care. CA Cancer J Clin, 56: 84-103, 2006.
6. Pessin H, Olden M, Jacobson C, Kosinski A: Clinical assessment of depression in terminally ill cancer patients: a pratical guide. Palliat Support Care, 3: 319-324, 2005.
7. Hotopf M, Chidgey J, Addington-Hall J, Lan Y: Depression in advanced disease: a systematic review. Part 1. Prevalence and case finding. Palliat Med, 16: 81-97, 2002.
8. Dein S: Psychiatric liaison in palliative care. Advances in Psychiatric Treatment, 9: 241-248, 2003.
9. Berney A, Stiefel F, Mazzocato C, Buclin T: Psychopharmacology in supportive care of cancer: a review for the clinicians. III. Antidepressant. Support Care Cancer, 8: 278-286, 2000.
10. Stockler MR, O'connell R, Nowak AK, Goldstein D, Turner J, Wilcken NR, Wyld D, Abdi EA, Glasgow A, Beale PJ, Jefford M, Dhillon H, Heritier S, Carter C, Hickie IB, Simes RJ: Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-bind randomised trial. Lancet Oncol, 8: 603-612, 2007.
11. Rodin G, Zimmermann C, Rydall A, Jones J, Shepherd FA, Moore M, Fruh M, Donner A, Gagliese L: The desire for hastened death in patients with metastatic cancer. J Pain Symptom Manage, 33: 661-675, 2007.
12. Serretti A, Artioli P: The pharmacogenomics of selective serotonin reuptake inhibitors. Pharmacogenomics J, 4: 233-244, 2004.
13. Kraft JB, Peters EJ, Slager SL, Jenkins GD, Reinalda MS, McGrath PJ, Hamilton SP: Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample. Biol Psychiatry, 61: 734-742, 2007.
14. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL: Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science, 274: 1527-1531, 1996.
15. Durham LK, Webb SM, Milos, PM, Clary CM, Seymour AB: The serotonin transporter polymorphism, 5-HTTLPR, is associated with a faster response time to sertraline in an elderly population with major depressive disorder. Psychopharmacology (Berlin), 174: 525-529, 2004.
16. Arias B, Catalán R, Gastá C, Gutiérrez B, Fañanás L: 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. J Clin Psychopharmacol, 23: 563-567, 2004.
17. Serretti A, Mandelli L, Lorenzi C, Pirovano A, Olgiati P, Colombo C, Smeraldi E: Serotonin transporter gene influences the time course of improvement of "core" depressive and somatic anxiety symptoms during treatment with SSRIs for recurrent mood disorders. Psychiatry Res, 149: 185-193, 2007.
18. Perlis RH, Mischoulon D, Smoller JW, Wan YJ, Lamon-Fava S, Lin KM, Rosenbaum JF, Fava M: Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. Biol Psychiatry, 54: 879-883, 2003.
19. Hu XZ, Rush AJ, Charney D, Wilson AF, Sorant AJ, Papanicolau GJ, Fava M, Trivedi MH, Wisniewski SR, Laje G, Paddock S, McMahon FJ, Manji H, Lipsky RH: Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. Arch Gen Psychiatry, 64: 783-792, 2007.
20. Zigmond AS, Snaith RP: The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand, 67: 361-370, 1983.
21. Costantini M, Musso M, Viterbori P, Bonci F, Del Mastro L, Garrone O, Venturini M, Morasso G: Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. Support Care Cancer, 7: 121-127, 1999.
22. Watson M, Law M, dos Santos M, Greer S, Baruch J, Bliss J: The Mini-Mac: further development of the Mental Adjustment to Cancer scale. J Psychosoc Oncol, 12: 33-46, 1994.
23. Grassi L, Buda P, Cavana L, Annunziata MA, Torta R, Varetto A: Styles of coping with cancer: the Italian version of the Mini-Mental Adjustment to Cancer (Mini-Mac) scale. Psychooncology, 14: 115-124, 2005.
24. Gelernter J, Kranzler H, Cubells JF: Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and

linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. Hum Genet, 101: 243-246, 1997.
25. Theobald DE, Kirsh KL, Holtsclaw E, Donaghy K, Passik SD: An open label pilot study of citalopram for depression and boredorm in ambulatory cancer patients. Palliat Support Care, 1: 71-77, 2003.
26. Schillani G, Capozzo MA, Aguglia E, De Vanna M, Grassi L, Conte MA, Giraldi T: 5-HTTLPR polymorphism of serotonin transporter and effects of sertraline in terminally ill cancer patients: report of eleven cases. Tumori, 94: 563-567, 2008.
27. Bandelow B, Andersen HF, Dolberg OT: Escitalopram in the treatment of anxiety symptoms associated with depression. Depress Anxiety, 24: 53-61, 2007.
28. Kim H, Lim SW, Kim S, Kim JW, Chang YH, Carroll BJ, Kim DK: Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. JAMA, 296: 1609-1618, 2006.
29. Cordova MJ, Giese-Davis J, Golant M, Kronnenwetter C, Chang V, McFarlin S, Spiegel D: Mood disturbance in community cancer support groups. The role of emotional suppression and fighting spirit. J Psychosom Res, 55: 461-467, 2003.