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Mental Adaptation to Cancer: Depression and Blood Platelet Monoamine Oxidase Activity in Breast Cancer Patients

TULLIO GIRALDI[1], MAURIZIO DE VANNA[1], MARIA MALAGOLI[2], GUIDO TUVERI[2], KATIA SUTTO[1], GIULIA SCHILLANI[1] and LUIGI GRASSI[3]

[1]*Dipartimento di Scienze Biomediche, Sezione di Farmacologia and Clinica Psichiatrica, Università di Trieste, I-34100 Trieste;*
[2]*Struttura Complessa di Oncologia, Azienda Opedaliera "Ospedali Riuniti", I-34100 Trieste;*
[3]*Section of Psychiatry, Department of Medical Sciences of Communication and Behaviour, University of Ferrara, I-44100 Ferrara, Italy*

Abstract. *Background: Stress and depression were reported as negative prognostic factors in breast cancer patients and monoamine oxidase (MAO) activity was considered a marker of mental suffering. Materials and Methods: MAO activity in platelets was determined in a group of newly diagnosed breast cancer patients, after the communication of diagnosis and surgery, using the Mental Adjustment to Cancer (MAC) and Hospital Anxiety and Depression scales (HADS). Results: The analysis of regression indicated that hopelessness-helplessness positively correlated with depression, anxiety and anxious preoccupation. Monoamine oxidase (MAO) activity displayed a positive regression coefficient with depression score. At follow-up, Cox analysis of survival indicated that MAO activity was a marginally significant risk factor. Conclusion: Further research in a larger group of patients may support the present results, showing that MAO activity is a biological marker of difficulties in mental adaptation to cancer and is a risk factor for survival.*

Extensive literature is available exploring the relationships between psychological factors and cancer incidence and progression. Numerous reports have indicated that, among the many factors considered, depression and stress might facilitate either the initial development of cancer or its subsequent growth and spread. In spite of their potential interest, these reports frequently possess methodological flaws, as well as difficulties in replication, which have been outlined and reviewed in depth by Fox (1) and other investigators (2).

Such difficulties may be limited when studies are designed in order to investigate the relationships between psychosocial factors and cancer progression after diagnosis and/or after initial treatment. This approach, which may be either prospective or retrospective, offers the advantage that all the subjects considered face a similar and challenging situation, namely coping with a potentially life threatening disease. A group led by Greer examined the modalities employed by 69 women with mammary carcinoma in their mental adaptation to the diagnosis of cancer in a 5-year prospective study. Recurrence-free survival was significantly higher for those patients who had initially reacted by denial or who had a fighting spirit, as compared with the patients who had responded with stoic acceptance or feelings of helplessness-hopelessness (3). Re-examination ten years after the patients' initial recruitment showed that the outcome for the patients with fighting spirit and denial was more favourable than that of the women showing stoic acceptance or the helpless-hopeless response; the type of psychological response was the most significant single factor among those considered (4, 5). A subsequent prospective survival study performed by the same group of investigators considered the effects of the psychological response on disease outcome in a larger cohort of 578 women with early-stage breast cancer. The psychological responses were measured using the Mental Adjustment to Cancer (MAC) scale and the Hospital Anxiety and Depression Scale (HADS). At 5-year follow-up, the Cox proportional hazards regression indicated a significantly increased risk of death in women with a high score on the depression sub-scale of HADS, and a significantly increased risk of relapse or death in women with high scores on the helplessness-hopelessness category of the MAC scale; there were no significant results for fighting spirit (6).

Correspondence to: Prof. Tullio Giraldi, Dipartimento di Scienze Biomediche, Sezione di Farmacologia, Università di Trieste, I-34100 Trieste, Italy. Tel: +39 040 5583537, Fax: +39 040 577435; e-mail: giraldi@units.it

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Table I. *Clinical characteristics of the study population.*

	N
Tumor size	
T0	1
T1 (equal or less than 2 cm)	5
T2 (more than 2 cm and less than 5 cm)	4
T3 (more than 5)	1
T4 (of any size, in touch with skin or thorax)	1
Nodal status	
Negative	3
Positive (N1)	8
Positive (N2)	1
Oestrogen receptor status	
Negative	9
Positive	3
Menopausal status	
Premenopausal	5
Postmenopausal	7
Metastasis	
Negative	9
Positive	3
Tumor stage	
Stage 1	4
Stage 2	2
Stage 3	1
Stage 4	4
Tumor histotype	
Infiltrating ductal carcinoma	6
Lobular infiltrating carcinoma	3
Ductal-lobular carcinoma	1
Pneumorform carcinoma	1
Squamous cell carcinoma	1
Surgery	
Quadrantectomy	6
Mastectomy	5
Biopsy only	1

Table II. *Basic descriptive statistics of the results of the psychometric evaluation of the 12 patients.*

Variable	Mean±SE	Median (quartiles)
HADS		
Depression	5.4±0.8	4.5 (3.25-7.75)
Anxiety	7.8±0.9	7.0 (5.25-9.75)
MAC		
Hopelessness helplessness	13.3±1.3	13.5 (10.0-15.0)
Fighting spirit	12.8±0.5	12.5 (11.25-14.0)
Anxious preoccupation	20.50±1.7	22.0 (15.0-24.0)
Avoidance	12.6±0.5	12.0 (11.25-13.75)

The role of depression, as identified using HADS, was also investigated by Walker *et al.* (7) in a prospective, randomised trial of 96 women with newly diagnosed large, or locally advanced, breast cancer. The response following primary chemotherapy was considered. The HADS depression score was a significant independent predictor of pathological response to chemotherapy, whereas the anxiety score was a significant independent predictor of clinical response.

The findings reported so far thus indicate that in women with early-stage breast cancer psychological factors, such as negative mental adaptation, may aggravate the progression of the disease. Depression can also modify the risk of death and the response to chemotherapy in women with previously untreated breast cancer.

Mental disorders, in particular depression, have been associated with alterations in monoaminergic cerebral neurotransmission and in particular with monoamine oxidase (MAO) activity. The initial discovery that iproniazid was a weak MAO inhibitor (MAOI) led to the widespread use of MAOIs as antidepressants in the early 1950s, to the subsequent development of selective agents in relation to the isoforms of the enzyme identified (MAO-A and MAO-B) and to the development of reversible inhibitors (8, 9). MAO activity has also been demonstrated in blood platelets and has been considered a marker of mental suffering (10, 11) and of the responsiveness to drug treatment in depressed patients (12).

The present investigation consequently had the aim of determining MAO activity in the blood platelets of peripheral blood in patients examined for their psychological response to newly diagnosed breast cancer.

Materials and Methods

Subjects and psychometric evaluation. The study population consisted of 12 consecutive subjects, with an average age of 56±15.3 years (median 59, range 32-75). The patients, referred to the Oncology Day Clinic of the General Hospital in Trieste from November 2002 until February 2003, were recruited after the communication of the cancer diagnosis and before the beginning of further treatment. The patients were found to be devoid of psychiatric symptoms or any previous psychiatric diagnosis, they were not receiving psychotropic medication (antidepressant drugs in particular) and had not smoked during the last two months preceding the initial assessment. The patients had a biopsy and those with a positive pathology requiring surgery received a diagnosis of mammary cancer, which was communicated by the same member of staff. The clinical characteristics of the patients and tumors are indicated in Table I.

Within two months after surgery, the patients were met and interviewed for psychological assessment and blood sampling. Before the interview, the patients expressed their informed consent for participation in the observational study and for the anonymous handling of the data. The psychometric instruments used were the MAC scale (13) and the HADS (14).

MAO activity assay. A 5 ml venous blood sample was collected from each patient in a Vacutainer^{R} containing EDTA as anticoagulant, and was maintained at 4°C until assay, which was performed within

Table III. *Analysis of the regression between the scores of the sub-scales of Mental Adjustment of Cancer (MAC), Hospital Anxiety and Depression scale (HADS), and mononoamine oxidase activity in the platelets of peripheral blood.*

	HADS		MAC				MAO
	Depression	Anxiety	Hopelessness helplessness	Fighting spirit	Anxious preoccupation	Avoidance	
HADS							
Depression		0.332	0.588*	–0.562*	0.395	–0.069	0.585*
Anxiety	0.332		0.670**	–0.271	0.598*	–0.576*	0.245
MAC							
Hopelessness helplessness	0.588*	0.670**		–0.513*	0.686**	–0.498*	0.301
Fighting spirit	–0.562*	–0.271	–0.513*		–0.252	0.425	0.025
Anxious preoccupation	0.395	0.598*	0.686**	–0.252		–0.706**	0.535
Avoidance	–0.069	–0.576*	–0.498*	0.425	–0.706**		–0.107

Each value in the table is the Spearman rho coefficient for the regression of the relevant variables. Mean significant regression, $*p<0.05$ or $**p<0.01$, respectively.

Table IV. *Cox regression analysis of survival of the patients with MAC and HADS scales' scores, and with MAO activity as covariate.*

	Chi-square	df	Sig.	B	SE	df	Sig.	Exp(B)	Lower CL	Upper CL
HADS A	6.455	1	0.011	0.419	0.268	1	0.118	1.520	0.899	2.570
MAO	2.979	1	0.084	0.170	0.111	1	0.127	1.185	0.953	1.474
MAC AP	2.890	1	0.089	0.164	0.104	1	0.115	1.178	0.961	1.443

Hospital Anxiety (HADS A) scale; Mental Adjustment to Cancer Scale; Anxious Preoccupation (MAC AP) scale; MAO: monoamine oxidase; B: hazard rate; Exp(B): anti-logarithm of hazard rate; CL: 95% confidence limits of Exp(B).

four hours. MAO activity was assayed according to the method of Mc Entire *et al.* (15). Platelet enriched plasma (PRP) was prepared by centrifugation of the blood sample at 300 xg for 20 min at 4°C and collection of the supernatant. The platelet number was determined with a Beckmann Coulter counter. A volume of 200 μl of PRP were added to 200 μl kinuramine (1.0 mM final concentration) and were incubated for 1 h at 37°C. The enzymatic activity was determined fluorimetrically (excitation at 318 nm and emission at 350 nm) measuring the formation of 4-hydroxyquinoline and was expressed as nmoles 4-hydroxyquinoline produced/10^8platelets/1 h.

Statistical analysis. The results were analyzed using the SPSS 10 statistical package for Windows (SPSS Italia, Bologna, Italy). The data were analyzed using non-parametric techniques (Spearman correlations) and the results at follow-up were analyzed using Cox proportional hazard analysis, as indicated in the tables.

Results

Most of the patients (pts) had T1 and T2 tumor size (5 and 4 pts respectively), a positive nodal status (9 pts) and no systemic metastases (9 pts). The TNM stage of the tumor was 1 and 4 for four patients each, the remaining being stage 2 or 3. Seven patients were postmenopausal, and nine had an estrogen receptor-negative tumor. The tumor histotype was infiltrating ductal carcinoma for six patients, lobular infiltrating carcinoma for three patients, the remaining three patients having different histotypes; the surgery performed was quandrantectomy for six patients and mastectomy for five.

The results of the psychometric evaluation of the patients are reported in Table II. When the scoring determined for each sub-scale of the HADS and MAC scales was analyzed by the Spearman regression test, the rho coefficients and the statistical significance obtained were as given in Table III. The hopelessness-helplessness scores of MAC displayed a significant negative coefficient with fighting spirit and with avoidance. Hopelessness-helplessness also displayed a positive significant correlation with anxious preoccupation (MAC), and with depression and anxiety of HADS sub-scale. When MAO activity was analyzed in relation to the psychometric scores, a positive and significant regression coefficient with the HADS depression score was observed.

The patients enrolled in this study were followed up for a period of 13-36 months; tumor recurrence and patients' deaths were analyzed using the Cox hazard analysis (Table IV). When tumor stage was considered as a single factor, it was a

significant covariate and constituted a risk factor for death of B=1.721. Among the psychological variables, HADS anxiety was a significant covariate, whereas MAO activity and MAC anxious preoccupation were close to significant.

Discussion

In the past, the levels of MAO activity have been considered as markers of mental disorders, in particular of depression, and of the response of depressed patients to treatment with MAO inhibitors as antidepressant drugs (16, 17). It is therefore interesting to note that the MAO activity measured in the present study was positively and significantly correlated with the values of the HADS depression sub-scale, which was positively correlated with hopelessness-helplessness and negatively with fighting spirit, which were identified as risk factors for disease progression, which is in agreement with other reports (6, 7).

These findings suggest the possibility that platelet MAO activity might be considered as a biological marker for mental suffering in cancer patients. Furthermore, a high MAO activity might also constitute an indication for psychotropic drug treatment with MAO inhibitors for these patients. Any differential involvement of the isoforms MAO-A or MAO-B, is an issue requiring future studies.

The role of MAO in the mental suffering of cancer patients was supported by the follow-up examination. The Cox proportional hazard analysis, as expected, indicated that in this group of patients the TNM stage represented a significant risk factor for survival. Moreover, in spite of the small number of patients investigated, anxiety was a significant covariate in the Cox analysis of survival, and MAO activity and anxious preoccupation were nearly significant. These findings are substantially in agreement with those initially reported by Greer and coworkers (4), showing that psychological factors, such as difficulties in mental adaptation to cancer, may be as significant for patient survival as clinical biological known risk factors are.

The presence of platelets in cancer deposits has been recognised for over a 100 years, and the link between cancer spread and platelet stimulation has been shown to be associated with the hypercoagulable state found in most cancer patients (18). The blood coagulation state has been studied as a therapeutic target for the inhibition of angiogenesis, tumor growth and metastasis, and treatment with antiplatelet drugs and anticoagulants has been suggested to provide significant benefits to cancer patients (19). The increase in activity of MAO observed in the platelets in the present study might therefore be considered as a psychobiological model, where platelets activated by difficulties in mental adaptation to cancer might contribute to increased tumor progression, as was observed at follow-up, to an almost significant statistical level.

The interpretation of the present results however requires caution because they are based on a limited number of patients and need validation in a larger sample, particularly for the role of MAO activity in relation to survival. Further research is also needed to elucidate whether the MAO activity was increased because of an adaptative reaction to the cancer diagnosis or of constitutive genetic characteristics of the patients. In this connection, the role of the functional polymorphism of the genes encoding for MAO enzymes should be considered, since the VNTR polymorphism in the regulatory region of the MAO A gene produces different levels of enzymatic expression and, for instance, shapes the development of antisocial behaviour in patients maltreated during their childhood (20). This work is currently in progress and will be reported once larger numbers of patients are available.

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