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Use of transfer factor in immunosuppressed surgical patients

Avaliação do uso de fator de transferência na resposta imunológica de pacientes cirúrgicos imunodeprimidos

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A B S T R A C T

Objective : *to evaluate the action of Transfer Factor on the immune response of patients with malignant neoplasm submitted to surgery, chemotherapy and radiotherapy.* **Method:** *we analyzed the variations of leukocytes, total lymphocytes, T-lymphocytes and CD4 counts in 60 patients submitted to immunostimulation with a single, daily dose of 0.5mg sublingual Transfer Factor, started simultaneously with chemotherapy and/or radiotherapy.* **Results:** *there were statistically significant increases in the counts of all cell lines studied, more pronounced after 12 months of use of the medication.* **Conclusion:** *the Transfer Factor restored immune response and showed no side effects.*

Keywords: Transfer Factor. Immunity, Cellular. Neoplasm Invasiveness.

INTRODUCTION

Discovered by Henry Sherwood Lawrence in 1955, the Transfer Factor (TF) is an extract obtained from calf splenic cells, consisting of a conjugated polypeptide with molecular weight around 6,000 Daltons and structure similar to the RNA[1-3]. TF has an important immune stimulatory function, promoting the maturation and differentiation of thymocytes in T lymphocytes, the restoration of function of malfunctioning peripheral lymphocytes, the recovery of humoral immunity through differentiation of B lymphocytes, forming plasmocytes and synthesizing specific humoral antibodies, the increase in allogeneic graft rejection capacity, the in vitro activation of T lymphocytes through cytotoxic action, lymphokine production and increased activity of the mononuclear phagocytic system. When administered orally, it establishes direct contact with the Peyer's plaques and lymph nodes, where it exerts a selective action on lymphocytes and antigen-presenting cells. Digestive enzymes and hydrochloric acid do not influence its stability[2-4].

The first evidence that cancer arises due to somatic genetic changes came from studies on Burkitt's lymphoma[4]. Since then, several malignancies have been associated with oncogens, with the possibility of using immunomodulators as a complementary treatment to surgery, chemotherapy and radiotherapy[5-10]. The best results of neoplastic disease treatment are achieved when surgery accomplishes the reduction of tumor load, complemented by chemotherapy and radiotherapy. However, these procedures affect the immune system, and even temporarily, influence the respective therapeutic regimens, which sometimes have to be interrupted due to the low number of leukocytes, lymphocytes and the important side effects resulting from impaired immune response. Immunostimulatory agents have contributed to avoid or minimize these collateral damages, among them the Transfer Factor, which was first used in the treatment of cancer by Fudenberg *et al.*[11] in 1976, and which has also been used in the treatment of non neoplastic diseases[2,3,11].

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METHODS

We carried out this study at the Gaffrée and Guinle University Hospital of the Federal University of the State of Rio de Janeiro – UNIRIO. We included 60 patients, both men and women, aged over 30 years, with malignant neoplasms, confirmed by histopathological examination of the surgical specimen, submitted to Chemotherapy (QT) and/or radiotherapy (RT) after surgery, and followed as outpatients for 12 months. We applied the immunostimulation with TF provided by the Laboratório de Extratos Alergênicos Ltda., registered with the Ministry of Health with the number 1729.0011.001-4. We administered the substance as a single dose of 0.5 mg sublingually daily and started concurrently with chemotherapy and/or radiotherapy. All patients underwent immunological evaluation prior to initiation of treatment by laboratory tests (leukocyte count, total lymphocytes, T lymphocytes, and CD4 lymphocyte subpopulation), which were repeated six and 12 months after initiation of therapy. We then compared those with the exams results before the beginning of treatment.

We present results as mean and standard deviation. We performed the data analysis using tables and graphs using the Microsft Office Excell7® software. For statistical analysis, we used Graph Pad Instat software version 3.0, San Diego California® and, for the purpose of interpretation, the type I error limit was up to 5% ($p < 0.05$). We tested the variables through the Kolmogorov-Smirnov (KS) method, inference through the Wilcoxon's test for non-parametric samples and the Student's t-test for parametric samples.

The study was evaluated and approved by the Ethics in Research Committee, in accordance with Resolution 196/96.

RESULTS

In the statistical analysis, all the samples evaluated had a normal distribution by the Kolmogorov and Smirnov (KS) method. The characteristics of the patients analyzed are contained in table 1.

Table 1. *Characteristics of the analyzed group.*

Gender		Age group – cases (%)		Tumor location – cases (%)	
Male	Female	30-39 years	96.7%) 4	Breast	20 (33.3%)
14 (23.3%)	60 (76.7%)	40-49 years	15 (25%)	Intestine	18 (30%)
		50-59 years	8 (13.3%)	Stomach	11 (18.3%)
		60-69 years	20 (33.3%)	Pancreas	5 (8.3%)
		+ 70 years	13 (21.7%)	Uterus	3 (5%)
				Lung	1 (1.7%)
				Liposarcoma	1 (1.7%)
				Kidney	1 (1.7%)

Regarding the total leukocyte count, 39 (65%) patients presented a 6-month increase in values and 50 (83.3%) in 12 months compared with the counts before the beginning of therapy. This increase ranged from 1.9% to 103% in six months, and from 2.1% to 170% in 12 months. We observed that of the 21 cases (35%) that had a reduction of the leukocyte values in six months, 18 (85.7%) were able to recover them in 12 months, and 12 (57.1%) achieved rates higher than before treatment.

The total lymphocyte count increased in six months in 40 (66.7%) patients and in 48 (80%) cases in 12 months. This increase ranged from 1.5% to 85% in six months and from 0.2% to 137.7% in 12 months. Of the 20 cases (33.3%) that had a reduction in lymphocyte values at six months, 16 (80%) were able to recover them in 12 months, 13 (65%) presenting higher values than those found at the beginning of treatment.

When analyzing the means of the leukocyte counts, we observed an increase of 5.6% when comparing the rates before treatment with those after six months, of 20.1% between pre-treatment and 12 months, and of 12.4% between six and 12 months of treatment. Regarding total lymphocyte means, this increase was 5%, 24.8% and 14.9%, respectively. Statistical analysis of these variations was very significant (Table 2).

Table 2. *Changes in the counts of leukocytes and lymphocytes.*

Leukocytes	Count	Lymphocytes	Count
Average		Average	
Before	5,073 (± 1281)	Before	1,642 (± 537)
6 months	5,356 (± 1522)	6 months	1,742 (± 580)
12 months	6,019 (± 1341)	12 months	1,980 (± 594)
T test	p < 0.0001	T test	p < 0.0001

Values expressed as mean ± standard deviation.

Table 3. *Changes in the counts of T and CD4 lymphocytes.*

T-Lymphocytes	Count	CD4-Lymphocytes	Count
Average		Average	
Before	1,174 (± 486)	Before	732 (± 279)
6 months	1,278 (± 463)	6 months	772 (± 311)
12 months	1,477 (± 541)	12 months	919 (316 ±)
T test	p < 0.0001	T test	p < 0.0001

Values expressed as mean ± standard deviation.

The analysis of T lymphocytes revealed that 38 (63.3%) patients presented an increase in counts at six months and 46 (76.7%) at 12 months in comparison with the result before the start of therapy. This increase ranged from 0.4% to 320% in six months and from 0.5% to 160% in 12 months. We observed that of the 22 cases (36.7%) that had a reduction in the T lymphocyte counts in six months, 17 (77.3%) were able to recover them in 12 months, and 11 (64.7%) achieved rates higher than before treatment.

As for the subpopulation of CD4 lymphocytes, there were also increases, in 35 (58.3%) cases when comparing the time treatment with six months, and in 51 (85%) between the time before treatment and 12 months. This increase ranged from 0.6% to 162.1% in six months and from 0.5% to 337.1% in 12 months. We observed that of the 25 cases (41.7%) that had CD4 subpopulation reduction in six months, 19 (76%) were able to recover them in 12 months, and 16 (84.2%) were able to obtain rates higher than before treatment.

When we evaluated the T-lymphocyte averages of the sample, we observed an increase of 8.8% when comparing the values before the start of treatment with those after six months, of 33.4% between pre-treatment and 12 months, and 15.6% between six and 12 months of treatment. The same was true for the CD4 subpopulation, with an increase of 5.5%, 20.6% and 19%, respectively. Statistical analysis of these variations was very significant (Table 3).

When we evaluated the means of the results in the studied period, we observed that in all of them there was an increase in values, which was more expressive after 12 months of treatment, as shown in figure 1.

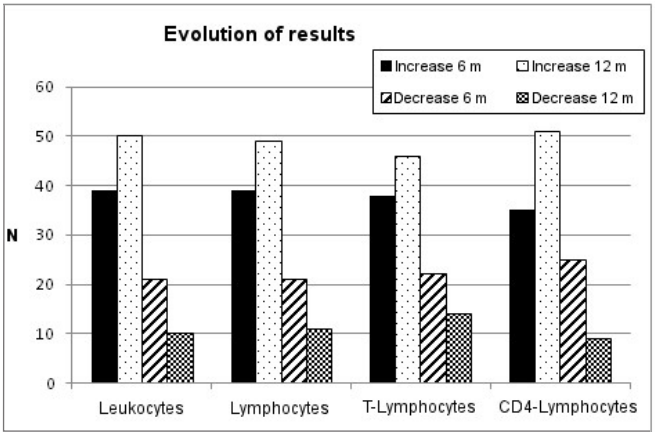

Figure 1. *Comparison of the results of the exams performed.*

DISCUSSION

A deficient immune response favors the appearance of several diseases of viral, bacterial and neoplastic origin. When it comes to cancer, this becomes more serious because the tumor itself, as well as the use of QT, RT and corticosteroids, also affects the immune system, further accentuating immunosuppression. Several immunomodulators have been used to reverse this situation with the aim not only of improving the immune response, minimizing the side effects of QT and RT, but of preventing the schedules used to be interrupted, which compromises treatment results[10-20].

The lymphocytes and their T subclasses are fundamental for the immune response, especially regarding solid tumors. Therefore, the combats to this type of tumor have the objective of making T-lymphocytes active and competent[16,17,19,20]. In this study, we observed that the total lymphocytes and their subclasses showed an increase in counts, which was more pronounced with TF use for 12 months, and even when counts fell in the first six months of treatment, these were recovered after 12 months. The best response was evidenced by the subpopulation of CD4-lymphocytes, with an increase of 80% at the end of the study, and among those who had an initial decrease, 76% of presented an increase with 12 months of treatment.

We also sought to analyze the effect of TF on total leukocytes, and we also observed an increase in counts in 83.3% of the cases with 12 months of therapy and, similar to lymphocytes, the 85.7% that had an initial reduction displayed higher rates after 12 months of TF use.

We conclude that TF promoted the activation of leukocytes, total lymphocytes and their subclasses, resulting in a stimulation of the immune response, specially when used for a period of 12 months.

R E S U M O

Objetivo: avaliar a ação do Fator de Transferência na resposta imunológica de pacientes portadores de neoplasia maligna submetidos à cirurgia, quimioterapia e radioterapia. **Método:** análise das variações dos valores dos leucócitos, linfócitos totais, linfócitos T e CD4 em 60 pacientes submetidos à imunoestimulação com Fator de Transferência administrado em dose única de 0,5mg por via sublingual, diariamente e iniciada simultaneamente à quimioterapia e/ou radioterapia. **Resultados:** houve um aumento no número de todas as linhagens celulares estudadas que foi mais acentuada após 12 meses de uso da medicação. A análise estatística realizada com o software *Graph Pad Instat*, testadas pelo método *Kolmogorov and Smirnov*, mostrou que os resultados foram significativos. **Conclusão:** o Fator de Transferência restabeleceu a resposta imune e não apresentou efeitos colaterais.

Descritores: Fator de Transferência. Imunidade Celular. Invasividade Neoplásica.

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