

Treatment of 741 italian patients with chronic fatigue syndrome

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Abstract. – BACKGROUND: Chronic Fatigue Syndrome (CFS) is a distinctive syndrome characterized by specific symptoms cluster. CFS mostly affects women and often results in severe functional limitation. Its prevalence varies from 0.4 to 2.5% in the general population. In our prior studies on the clinical features of 205 CFS patients we founded immunological and brain abnormalities. In this paper we illustrate our caseload on CFS treatment.

PATIENTS AND METHODS: From January 2000 to December 2005, we evaluated all the patients admitted at the CFS Unit of the Aviano National Cancer Institute, for staging procedures and treatments. Patients not meeting the Fukuda diagnostic criteria were excluded.

RESULTS: 250 male and 491 female (median age 35.5 and 39.3 years, respectively) were enrolled and treated for CFS. As expected, CFS resulted from previous infectious disease in all patients. Female patients showed to be more affected by symptoms than male patients. The treatment schedules followed by the patients included nutritional supplements alone, corticosteroids, antidepressant/sedative drugs, and antiviral/immunoglobulin drugs. Antiviral/immunoglobulin drugs achieved the best response (15.3% positive responses vs. 8.3% negative responses; OR 0.44, CI 0.26-0.74, $p = 0.002$). The carrying out of 4 or more treatments showed a protective effect (OR 0.46, CI 0.28-0.77, $p = 0.003$). This finding was confirmed in the multivariate analysis, adjusted by type of drugs (OR 0.49, CI 0.28-0.84, $p = 0.009$) and number of treatments carried out (OR 0.51, CI 0.30-0.86, $p = 0.01$); these two variables were independent.

CONCLUSIONS: These findings show that the antiviral/immunoglobulin approach has a longer positive disease free survival in comparison with other approaches. However, CSF still remains a difficult disease to be effectively treated.

Key Words:

Chronic fatigue syndrome, CSF, CFS, Fatigue, Treatment.

Introduction

In 1994, among the International Chronic Fatigue Study Group, Fukuda et al¹ contributed to formulate the diagnostic criteria defining a particular syndrome characterized by a symptoms cluster, and named chronic fatigue syndrome (CFS). It mainly consists of persistent or recurrent fatigue usually associated with post-exertional malaise, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain without joint swelling or redness, headaches, unrefreshed sleep, and self-reported impairment of short-term memory or concentration severe enough to have substantial impact on a patient's occupation, education, or personal activities.

We have studied the clinical features of CFS in the first series of 205 Italian patients in 1993², and we had found immunological abnormalities³, and brain abnormalities⁴.

The prevalence of CFS varies from 0.4 to 2.5% in the general population, it particularly affects women, and often results in severe functional limitation⁵. So, CFS represents a huge problem for contemporary health care due to the high direct as well as indirect medical and social costs⁶.

In this paper we illustrate our large case load on CFS.

Patients and Methods

From January 2000 to December 2005, we evaluated all the patients admitted at the CFS Unit of the Aviano National Cancer Institute, North-Eastern of Italy, for CFS staging procedures. Patients meeting the diagnostic criteria formulated by the Centers for Disease Control and prevention (CDC)¹ were enrolled. To identify medical conditions considered exclusionary for CFS, the clinical evaluation included a standardized past medical

history, a standardized physical examination, and a routine laboratory testing of blood and urine. Patients previously diagnosed with autoimmune disorders, psychiatric disorders, epilepsy, heart diseases, tumours, or who were pregnant or breast-feeding were excluded.

As the knowledge on the best therapy for CFS was ongoing during the enrolment period, patients received several different treatments according to the best clinical practice of the time. Treatments, prescribed as single agent or combinations thereof, included different classes of drugs: nutritional supplements (such as vitamins B2 and B12, minerals, amino acids, and fatty acids), corticosteroids, antiviral drugs (i.e., methisoprinol), immunoglobulins, antidepressants, and sedatives drugs.

Drugs were changed according to patients' response to therapy or when there was an intolerance to the drug given.

Treatments response was evaluated by investigators at 3/6 month intervals. As the patients would have received different drugs during the observation period, we assigned an overall treatment

response for each patient assessing which drug maintained the longest response, and according to the drug schedule.

A global assessment of efficacy of treatments for each patient was assigned on the basis of which drug was given the longest response.

All the clinical data (age of patients, duration and aetiology of fatigue, type of associated symptoms, type of treatments) were collected from medical records.

Statistical Analysis

At enrolment time point, some data were missing because of sampling and/or technical gaps. All analyses were carried out with SAS 9.2 statistical software (SAS Institute, Inc., Cary, NCI). Difference between subgroups of qualitative variables were assessed by chi-square test⁷. Odds ratios (OR) and 95% confidence intervals (CIs) were evaluated by unconditional multiple logistic regression model adjusted for the majors confounding factors⁸. Results were considered statistically significant at a 2-tailed *p* value ≤ 0.05.

Table I. Distributions of some clinical characteristics of 741 patients with chronic fatigue syndrome (CFS) according to gender.

	Male (N = 250)		Female (N = 491)		Chi-square test <i>p</i> -value
	N	(%)	N	(%)	
Age (years) ¹					
< 40	150	(62.2)	262	(55.7)	0.10
≥ 40	91	(37.8)	208	(44.3)	
Median (range)	35.5 (14-76)	38.3 (10-75)			
Fatigue duration					
< 6 months	5	(2.0)	7	(1.4)	0.55
≥ 6 months	245	(98.0)	484	(98.6)	
Presence of symptoms (yes)					
Fever	99	(39.6)	255	(51.9)	0.002
Muscle pain	109	(43.6)	274	(55.8)	0.002
Multi-joint pain	87	(34.8)	233	(47.5)	0.001
Sore throat	32	(12.8)	86	(17.6)	0.10
Impaired memory/concentration	91	(36.4)	195	(39.7)	0.38
Headaches	21	(8.4)	62	(12.6)	0.08
Tender cervical/axillary lymph nodes	13	(5.2)	32	(6.6)	0.48
Sleep disorders	48	(19.2)	104	(21.2)	0.53
Post exertional malaise	51	(20.4)	132	(26.9)	0.05
Aetiology of fatigue infectious disease (ID) alone	137	(54.8)	310	(63.1)	
ID and vaccine	4	(1.6)	9	(1.8)	0.14
ID and toxic substances exposure	45	(18.0)	77	(15.7)	
ID and other causes	64	(25.6)	95	(19.6)	
Type of treatment					
Supplements alone	95	(38.0)	146	(29.7)	0.03
Corticosteroids	100	(40.0)	229	(46.6)	
Antidepressant/sedative	31	(12.4)	47	(9.6)	
Antiviral/immunoglobulin	24	(9.6)	69	(14.1)	

¹The sum does not add up to the total because of some missing.

Table II. Distributions of schedule and years of treatment of 741 patients with chronic fatigue syndrome (CFS) according to type of drugs.

Treatment schedule/years	Type of drugs			
	Supplements alone N. (%)	Corticosteroids N. (%)	Antidepressant/ sedative N. (%)	Antiviral/ immunoglobulin N. (%) ¹
I treatment schedule				
1996-2001	93 (49.2)	79 (41.8)	13 (6.9)	4 (2.1)
2002-2003	128 (44.4)	120 (41.7)	28 (9.7)	12 (4.2)
2004-2005	92 (35.0)	96 (36.5)	23 (8.7)	52 (19.8)
Chi-square test (df); <i>p</i> -value		58.25 (6); <i>p</i> < 0.0001		
II treatment schedule				
1996-2001	32 (35.6)	36 (40.0)	13 (14.4)	9 (10.0)
2002-2003	46 (41.8)	48 (43.6)	8 (7.3)	8 (7.3)
2004-2005	29 (24.2)	37 (30.8)	21 (17.5)	33 (27.5)
Chi-square test (df); <i>p</i> -value		30.47 (6); <i>p</i> < 0.0001		
III treatment schedule				
1996-2001	13 (38.2)	10 (29.4)	6 (17.7)	5 (14.7)
2002-2003	22 (39.3)	22 (39.3)	6 (10.7)	6 (10.7)
2004-2005	15 (23.8)	17 (27.0)	14 (22.2)	17 (27.0)
Chi-square test (df); <i>p</i> -value		10.99 (6); <i>p</i> = 0.09		
IV treatment schedule				
1996-2001	4 (23.6)	7 (41.2)	3 (17.6)	3 (17.6)
2002-2003	18 (45.0)	9 (22.5)	3 (7.5)	10 (25.0)
2004-2005	4 (15.4)	9 (36.0)	8 (57.2)	12 (48.0)
Chi-square test (df); <i>p</i> -value		13.41 (6); <i>p</i> = 0.04		
V treatment schedule				
1996-2001	2 (25.0)	2 (25.0)	4 (50.0)	—
2002-2003	5 (27.8)	6 (33.3)	2 (11.1)	5 (27.8)
2004-2005	2 (9.5)	6 (28.6)	4 (19.0)	9 (42.9)
Chi-square test (df); <i>p</i> -value		9.64 (6); <i>p</i> = 0.14		

¹Row percentage.

Results

Table I shows the distributions of the clinical characteristics recorded at the enrolment time of the 741 patients, 250 male and 491 female (with a median age of 35.5 years and 39.3 years, respectively) treated for CFS at our Institute between January 2000 and December 2005. We decided to include in our analysis the 12 patients that were affected by fatigue for a shorter period than the requested six months of the Fukuda et al diagnostic criteria because they fulfilled all the other criteria, and also because the fatigue was present for 5 months anyway.

Male and female patients did not differ for age (median was 35.5 years and 39.3 years, respectively), duration of fatigue and aetiology of fatigue. As expected, CFS was the result of a previous infectious disease for all the patients; only 13 patients reported they were also vaccinated just before experiencing CFS, while exposure to toxic substance happened to about 18% of the

patients. As regards the presence of the mostly associated symptoms with fatigue according to Fukuda et al, female patients showed to be more affected by symptoms than male patients¹.

Additionally, we found a statistically significant difference between the two gender groups in four symptoms: fever (*p* = 0.002), muscle pain (*p* = 0.002), multi-joint pain (*p* = 0.001), and post exertional malaise (*p* = 0.05).

Table II shows the distributions of the treatment schedule followed by the patients. Treatments, prescribed as single agent or combinations thereof, were pooled in four subgroups during the statistical analysis: nutritional supplements alone, corticosteroids, antidepressant/sedative drugs, and antiviral/immunoglobulin drugs. Some medical records reported previous treatments prescribed by our team before year 2000, so we decided to include that information in our analysis. First choice of drugs was nutritional supplements alone or corticosteroids in every considered period of years; instead, the use of

antiviral/immunoglobulin drugs showed an increasing trend from 1996-2001 years to 2004-2005 years (2.1% vs. 19.8%, respectively). This trend was confirmed also in the second and following treatment schedules.

Table III shows the overall response to treatments and their odds ratios (OR). Even if young female showed the best response, in the univariate analysis age and gender showed not to statistically differentiate the patients. Among the treatments, antiviral/immunoglobulin drugs achieved the best response for the treatment of CFS (15.3% of positive responses vs. 8.3% of negative responses) in the univariate analysis (OR 0.44, CI 0.26-0.74, $p = 0.002$). Further, carrying out 4 or more treatments showed to have a protective effect (OR 0.46, CI 0.28-0.77, $p = 0.003$). This result was confirmed also in the multivariate analysis, adjusted by type of drugs (OR 0.49, CI 0.28-0.84, $p = 0.009$) and number of treatments carried out (OR 0.51, CI 0.30-0.86, $p = 0.01$): these two variables were independent.

Table IV shows the hazard ratios of the disease free of the 741 patients with CFS. Every type and the number of treatment carried out showed to have a protective effect on CFS, with antiviral/immunoglobulin drugs and 4 or more treatments the best results. The multivariate analysis confirmed a positive effect only for the treatment antiviral/immunoglobulin drugs (HR 0.62, CI 0.40-

0.98, $p = 0.04$), and the best effect for 4 or more treatments (HR 0.14, CI 0.09-0.22, $p < 0.001$). See also Figure 1 and Figure 2.

Discussion

The treatment of CFS is matter of debate among clinicians dealing with this disorder. The course of CFS is highly fluctuating, with alternating periods of improvement and deterioration. Many pharmacological therapies have been used for treating CFS. However, there are very few publications on randomized clinical trials with drugs and there is no standard therapy for these patients so far⁹⁻¹¹.

Our experience, started before 2000, is one of the largest series in literature: it reflects the evolution of the knowledge on CFS and its treating approach.

According to the knowledge of the time¹²⁻¹⁴, we started to treat CFS patients with nutritional supplements, alone or in combination thereof, as the first choice, whereas corticosteroids were the second one. Our results showed mixed and not conclusive responses to these treatments.

As Van Houdenhove et al¹⁵ have illustrated in their recent review, the use of antidepressant and sedative drugs showed not to be curative for the CFS, although they were useful for some sympto-

Table III. Odds ratios (OR) and 95% confidence intervals (CIs) of gender, age, type of drugs and number of treatment of 741 patients with chronic fatigue syndrome (CFS) according overall response.

	Overall response		Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
	No N. (%)	Yes N. (%)				
Gender						
Male	107 (36.9)	143 (31.7)	12			
Female	198 (63.1)	308 (68.3)	0.79 (0.58-1.07)	0.13		
Age (years)¹						
< 40	153 (55.0)	259 (59.8)	12			
≥ 40	125 (45.0)	174 (40.2)	1.22 (0.90-1.65)	0.20		
Type of drugs						
Supplements alone	107 (36.9)	134 (29.7)	12		12	
Corticosteroids	126 (43.4)	203 (45.0)	0.78 (0.56-1.09)	0.14	0.85 (0.60-1.20)	0.36
Antidepressant/sedative	33 (11.4)	45 (10.0)	0.92 (0.55-1.54)	0.75	1.03 (0.61-1.74)	0.92
Antiviral/immunoglobulin	24 (8.3)	69 (15.3)	0.44 (0.26-0.74)	0.002	0.49 (0.28-0.84)	0.009
N. treatment						
1	177 (61.1)	243 (53.9)	12		12	
2	67 (23.1)	100 (22.1)	0.92 (0.64-1.33)	0.65	0.98 (0.68-1.42)	0.91
3	23 (7.9)	40 (8.9)	0.79 (0.46-1.37)	0.40	0.86 (0.49-1.51)	0.61
≥ 4	23 (7.9)	68 (15.1)	0.46 (0.28-0.77)	0.003	0.51 (0.30-0.86)	0.01

¹The sum does not add up to the total because of some missing. ²Reference category.

Table IV. Hazard ratio and 95% confidence intervals (CIs) of disease free 741 patients with chronic fatigue syndrome (CFS) according to type of treatment and number of treatment.

	N.	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Gender					
Male	250	12			
Female	491	0.81 (0.64-1.04)	0.09		
Age (years)¹					
< 40	412	12			
≥ 40	299	1.18 (0.93-1.49)	0.18		
Type of treatment					
Supplements alone	241	12		12	
Corticosteroids	329	0.65 (0.50-0.84)	0.001	0.93 (0.72-1.22)	0.61
Antidepressant/sedative	78	0.67 (0.45-0.99)	0.04	1.03 (0.69-1.53)	0.88
Antiviral/immunoglobulin	93	0.39 (0.25-0.61)	< 0.001	0.62 (0.40-0.98)	0.04
N. of treatment					
1	420	12		12	
2	167	0.50 (0.37-0.66)	< 0.001	0.51 (0.39-0.68)	< 0.001
3	63	0.27 (0.27-0.42)	< 0.001	0.28 (0.18-0.43)	< 0.001
≥ 4	91	0.13 (0.08-0.20)	< 0.001	0.14 (0.09-0.22)	< 0.001

¹The sum does not add up to the total because of some missing. ²Reference category.

matic patients with co-morbid anxiety and depression symptoms. On the contrary, our findings demonstrate that antiviral/immunoglobulin therapies had the better response for the treatment of CFS (15.3 positive responses), in comparison with the other therapies. Moreover, the impact on disease free survival was clearly superior.

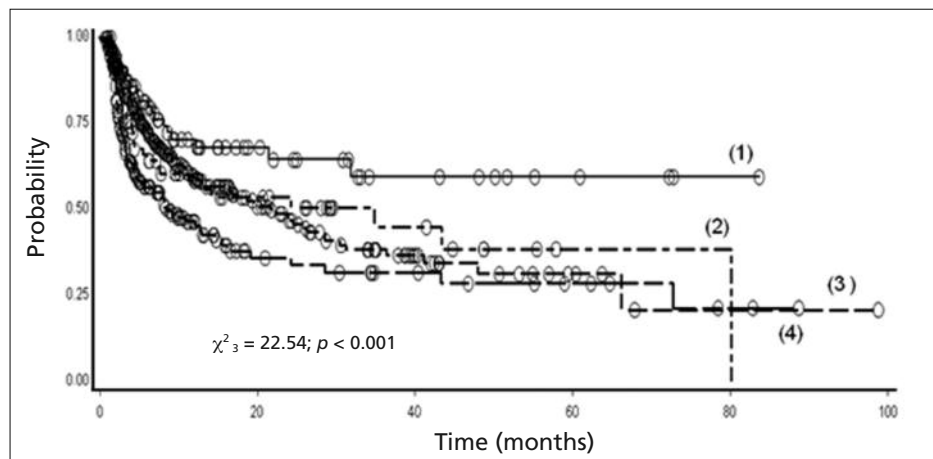
Although these data are based on a retrospective evaluation, the fact that we are dealing with 741 patients is quite important in order to have sufficient strength for the conclusion of this report. However we need prospective evaluation of these different therapies because CSF is a group of different diseases with probably different etiopathogenetic features: for example, CFS may occurs after infectious agents, like the patients of our study,

as well as a cancer disease. In fact, as we have previously suggested, we believed that also the chronic/persistent fatigue experience by long-term cancer survivors may be another manifestation of CFS needing further studies¹⁶.

Conclusions

CSF remains a difficult disease to be treated effectively, but our results show that a significant number of patients treated with antiviral/immunoglobulin approaches have a long positive disease free survival in comparison with other patients treated with the other approaches (i.e., antidepressants, corticosteroids, and supplements).

Figure 1. Disease free survival of 741 patients with chronic fatigue syndrome (CFS) according to type of treatment (1 = Antiviral/immunoglobulin; 2 = Antidepressant/sedative; 3 = Corticosteroids; 4 = Supplements alone).



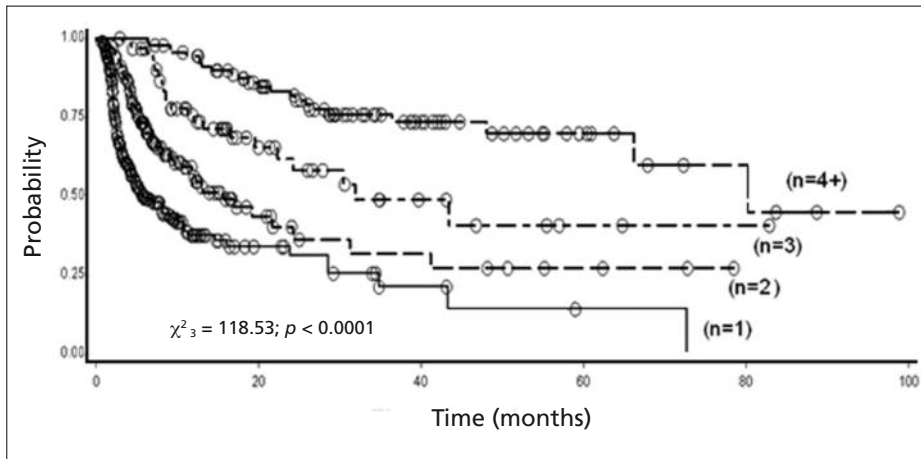


Figure 2. Disease free survival of 741 patients with chronic fatigue syndrome (CFS) according to number of schedule/cycles of treatment.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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