The Effects of IFN-α and 13-CRA on the Cognitive Function of Adults with Aggressive Squamous Cell Carcinoma

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Abstract

Interferon alpha (IFN) and 13-cis retinoic acid (CRA) are currently used in combination for the treatment of advanced squamous cell carcinoma (SCC). CRA is not associated with significant side effects but IFN has been consistently associated with the induction of depression and, to a lesser extent, cognitive impairment (e.g., memory, executive functioning, and verbal fluency). The purpose of the present study was to more fully characterize the effects of IFN on mood and cognitive functioning in a sample of 54 patients with advanced SCC. Following baseline neuropsychological assessment, patients were randomized to IFN+CRA or observation and underwent follow-up assessment after 3 months treatment. It was predicted that patients undergoing treatment would evidence declines in verbal memory, executive functioning, and verbal fluency, and demonstrate increased depression symptoms and decreased quality of life relative to patients randomized to observation. Analyses were made with repeated measures ANCOVAs (p<0.05 for primary hypotheses and p<0.01 for secondary hypotheses). Small differences were demonstrated following 3-months of treatment across domains of verbal fluency and executive functioning. Increases in depressive symptoms and a greater endorsement of general cancer concerns were also noted following IFN+CRA treatment. No differences were found on additional measures of cognitive functioning. Effect sizes were small, though nearly all cognitive measures were in a pattern consistent with IFN+CRA either impairing performance, or suppressing practice effects, relative to patients in the observation condition. The sum of the effects suggest diffuse but meaningful alterations in functioning (cognitive and mood) and are generally consistent with frontal-subcortical dysfunction.

Introduction

Squamous cell carcinoma of the head and neck is relatively common and associated with significant morbidity. Interferon-α (IFN) and 13-cis-retinoic-acid (13-CRA) are used as a combination treatment for squamous cell carcinoma (Lippman et al, 1992). Patients treated with IFN-α frequently evidence increases in depression and, to a lesser extent, cognitive impairment (e.g., verbal memory, executive functioning, verbal fluency) (Scheibel et al., 2004). The literature assessing the effects of IFN is limited, however, as most studies are retrospective, do not account for baseline differences, or fail to use appropriate measures for assessing neuropsychological impairment. The purpose of the present study was to more fully characterize the effects of IFN on mood and cognitive functioning in a sample of 54 patients with advanced SCC using a randomized, pretest-posttest design. It was predicted that patients undergoing treatment would evidence declines in verbal memory, executive functioning, and verbal fluency, and demonstrate increased depression symptoms and decreased quality of life relative to patients randomized to observation.

Method

Data were obtained from 64 patients diagnosed with squamous cell carcinoma of the head and neck and participating in an IFN+CRA protocol at MD Anderson Cancer Center, Houston, Texas. Patients underwent baseline neuropsychological testing and then while on treatment at 3-months. Patients completed primary measures, including the Hopkins Verbal Memory Test-Revised (HVLT), Controlled Oral Word Association (COWA), Trail Making Test Part B (TMT B), Beck Depression Inventory-II (BDI), and the Functional Assessment of Cancer Therapy with Head and Neck subscale (FACT-HN). Secondary measures included Digit Span and Digit Symbol tests, Trail Making Test Part A (TMT A), Grooved Pegboard test, and the State Trait Anxiety Inventory (STAI). ANCOVAS were made for raw scores on each test, with age, education, BDI, and gender included as covariates if significant with the dependent measure ($p \leq 0.10$). Primary measures were assessed at $p < 0.05$, whereas secondary measures were assessed at $p < 0.01$. Unless otherwise noted, data for all measures met ANCOVA assumptions. Effect sizes (Cohen's d) were calculated, with a predetermined level of d ≥ 1.0 indicating clinically significant change

Results

A total of 64 patients were initially enrolled into the study. Of these patients, only 54 were available for follow-up assessment at 3 months (26 treatment and 28 observation). A one-way ANOVA demonstrated no differences in age and education between the remaining sample and patients who failed to return for follow-up ($p > 0.05$). Of the remaining sample, there were no significant between group differences with regard to age and education ($p > 0.05$). There were only four women enrolled in the study and by chance they were all randomized to the observation arm. Overall the sample was older, well educated, predominantly male, and entirely Caucasian (see Table 1). Primary measures are presented in Table 2. There was a significant main effect for treatment for the COWA and significant treatment-by-time interactions for TMT-B, BDI, and FACT-G. There were no significant differences among secondary cognitive measures (Table 3). Effect sizes with signs indicating relative improvement for each treatment group are depicted in Figure 1 and none exceeded d ≥ 1.0 .

Table 1. Demographic Characteristics of the Sample

	IFN+CRA (n=26)		Observation (n=28)	
Characteristic	Mean	SD	Mean	SD
Age (years)	60.5	11.5	63.2	13.7
Education	12.5	2.5	13.1	3.3
	n	*%*	*n*	*%*
Gender				
Male	26	100	24	86
Female	0	0	4	14
Race				
White	26	100	28	100

Table 2. Average Raw Scores on Primary Measures

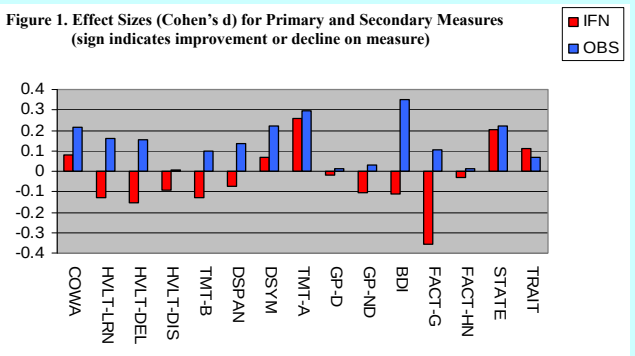
	Baseline	Follow-up
COWA[a]		
IFN	26.2 (8.9)	26.9 (8.3)
OBS	31.8 (9.3)	33.8 (11.7)
HVLT		
Learning		
IFN	20.5 (5.4)	19.8 (6.0)
OBS	20.4 (5.6)	21.3 (4.8)
Delay		
IFN	6.7 (2.6)	6.3 (2.7)
OBS	6.8 (2.6)	7.2 (2.7)
Discrimination		
IFN	10.6 (1.3)	9.7 (2.5)
OBS	10.4 (1.5)	10.5 (1.1)
TMT B[b,c]		
IFN	103.5 (62)	115.5 (66)
OBS	121.6 (66)	115.0 (66)
BDI[b]		
IFN	8.6 (6.2)	9.3 (6.2)
OBS	9.8 (7.9)	7.0 (7.5)
FACT		
General[b]		
IFN	89.1 (12.1)	84.8 (16.1)
OBS	88.1 (16.0)	89.8 (13.4)
Head and Neck		
IFN	29.1 (5.1)	27.6 (5.4)
OBS	27.0 (7.1)	27.1 (7.5)

Note. [a] indicates main effect for treatment. [b] indicates treatment-by-time interaction. [c] indicates transformed data.

Table 3. Average Raw Scores on Secondary Measures

	Baseline	Follow-up
Digit Span		
IFN	13.2 (4.0)	12.9 (4.1)
OBS	13.0 (2.9)	13.4 (3.0)
Digit Symbol		
IFN	38.8 (12.7)	39.7 (11.4)
OBS	39.5 (12.6)	42.3 (12.7)
Grooved Pegboard		
Dominant		
IFN	91.4 (34)	92.0 (40)
OBS	92.5 (32)	92.1 (32)
Non-Dominant		
IFN	97.5 (41)	101.7 (39)
OBS	101.3 (33)	100.2 (32)
TMT A[c]		
IFN	43.3 (16.2)	40.5 (20.1)
OBS	46.6 (27.5)	42.5 (33.4)
STAI		
State		
IFN	32.0 (9.8)	30.0 (9.7)
OBS	34.8 (11.1)	32.0 (9.9)
Trait		
IFN	32.9 (10.6)	31.7 (9.0)
OBS	34.5 (11.4)	33.7 (10.5)

Figure 1. Effect Sizes (Cohen's d) for Primary and Secondary Measures (sign indicates improvement or decline on measure)



Discussion

In the present study, small differences were demonstrated following 3-months of treatment across domains of verbal fluency and executive functioning along with increased depressive symptoms and greater endorsements of general cancer concerns. No differences were found on additional measures of cognitive functioning. Effect sizes were small, though nearly all cognitive measures were in a pattern consistent with IFN either impairing performance, or suppressing practice effects, relative to patients in the observation condition. While individual ES were not clinically significant, the sum of the effects suggest diffuse but meaningful alterations in functioning (cognitive and mood) and are generally consistent with frontal-subcortical dysfunction. Although speculative, the small effects may be related to comparatively low IFN dose used in this study. Lastly, these data need to be assessed in the context of the actual benefit of IFN-CRA on SCC.

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