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Original Paper

The Cognitive Effects of Recombinant Interleukin-2 (rIL-2) Therapy: a Controlled Clinical Trial Using Computerised Assessments

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It has been suggested that patients undergoing treatment with recombinant interleukin-2 (rIL-2) may develop cognitive impairment. To evaluate these effects, 17 patients with advanced colorectal cancer took part in a randomised, parallel group study of rIL-2 with chemotherapy (5-fluorouracil and leucovorin) and chemotherapy alone. Assessments were carried out daily whilst patients were in hospital and regularly between cycles of treatment using state-of-the-art computerised cognitive assessment, as well as traditional psychometric tests. Rigorous discontinuation criteria were applied to ensure that the effect of time-related variables did not influence the results. One patient developed repeated transient psychotic episodes associated with rIL-2 infusions and another regularly became confused. Computerised cognitive assessments revealed that immunochemotherapy produced significant impairment in various tasks, especially reaction time, picture recognition and vigilance. These effects were not due to sleep deprivation or pyrexia. For most patients, cognitive functioning was restored to the baseline level within 10 days following the cessation of rIL-2. In conclusion, during infusions of rIL-2, some patients experience severe confusion and amnesia which resembles some of the major cognitive impairments associated with dementias such as Alzheimer's disease. Computerised cognitive assessment using the Cognitive Drug Research system provides a feasible, sensitive and reliable method of evaluating cognitive changes in patients with cancer. It could usefully be included in quality of life assessments in clinical trials where treatment-related cognitive changes need to be evaluated.

Key words: interleukin-2 therapy, psychoneuroimmunology, cognition, mood, biological response modifier, psychosocial oncology

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INTRODUCTION

INTERLEUKIN-2 (IL-2) is a 15.5 kDa glycoprotein secreted by T-helper lymphocytes following activation by antigens or mitogens. It enhances various aspects of host defences including natural cytotoxicity mediated by natural killer (NK) and lymphokine-activated killer (LAK) cells, which are believed to be important anticancer defence mechanisms. Recombinant IL-2 (rIL-2) has been used to inhibit tumour growth in experimental animal models and, with less success, therapeutically in man [1]. Unfortunately, when given systemically and in high doses, most patients experience a 'flu-like' illness as well as developing a number of specific cardiopulmonary, renal, gastrointestinal, haematological, dermatological and other side-effects. Consequently, in many instances (systemic therapy, high doses), patients require hospitalisation for treatment. There is a growing awareness of the importance of evaluating the effects of new therapies on quality of life, particularly in patients with

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advanced cancer. Uncontrolled studies have suggested that rIL-2 may have a number of adverse effects, including marked changes in cognitive and emotional functioning.

Denicoff and associates [2] studied the effects of rIL-2 and LAK cells in 44 patients with metastatic cancer. 15 (34%) developed severe changes in behaviour necessitating acute intervention and 22 (50%) became disoriented and showed impairment on cognitive tests. However, the cognitive changes were reversible.

In a study of 7 patients receiving continuous rIL-2 therapy, tumour-infiltrating lymphocytes and chemotherapy for metastatic melanoma, Caraceni and associates [3] found impaired performance on tests of orientation, spatial memory and attention. However, the validity of their statistical analysis is questionable because they used the Mann–Whitney test to analyse their data despite the fact that, in some cases, repeated measures were used for the same subjects. They also noted increased latency and decreased amplitude of the P300 auditory evoked EEG potential.

Smith and Khayat [4] reported 2 cases of malignant melanoma where rIL-2 and alpha-interferon therapy were associated with transient, predominantly hallucinatory, confusional syndromes occurring, or persisting, several days after cessation of therapy.

Although lower doses of rIL-2 delivered intermittently by the subcutaneous route have been found to be less toxic, the psychosocial effects have not been evaluated. The perceived morbidity of systematically administered rIL-2 therapy has restricted its use by some clinicians, particularly in combination with other anticancer agents. However, previous studies assessing rIL-2 toxicity have suffered from various methodological problems including the absence of an appropriate comparison group to control for the possible effects of sleep deprivation, hospitalisation, diet, exercise and concomitant use of other drugs. They have also used relatively insensitive psychometric instruments.

Therefore, we devised a prospective, randomised controlled study in patients undergoing rIL-2 therapy for advanced colorectal cancer. An intensive, reliable and highly sensitive computerised method of cognitive assessment and psychometric evaluation of various other aspects of psychological functioning was undertaken, as well as self-reporting of side-effects.

PATIENTS AND METHODS

Design

Figure 1 shows the basic trial design for the first 3 months of therapy. Patients were allocated at random to immunochemotherapy or chemotherapy alone. Immunochemotherapy was carried out in 4-week cycles and consisted of 18×10^6 IU/m^2/24 h of rIL-2 infused continuously by the intravenous route over 5 days (120 h); 5-fluorouracil (5-FU) (600 mg/m^2) and leucovorin (LV) (25 mg/m^2) were administered 48 h later following the cessation of rIL-2 infusion and then repeated at weekly intervals on two further occasions. Chemotherapy, consisting of identical doses of 5-FU and LV, was administered weekly for 6 weeks followed by a rest period of 2 weeks. Patients receiving immunochemotherapy or chemotherapy could receive therapy for up to 6 months depending on tumour response to treatment.

Patients in both groups spent the first 8 days of each cycle in hospital (to control for sleep deprivation and hospitalisation); in both groups, blood pressure, pulse and temperature were monitored hourly for the first 120 h. In addition, chemotherapy patients were hospitalised during

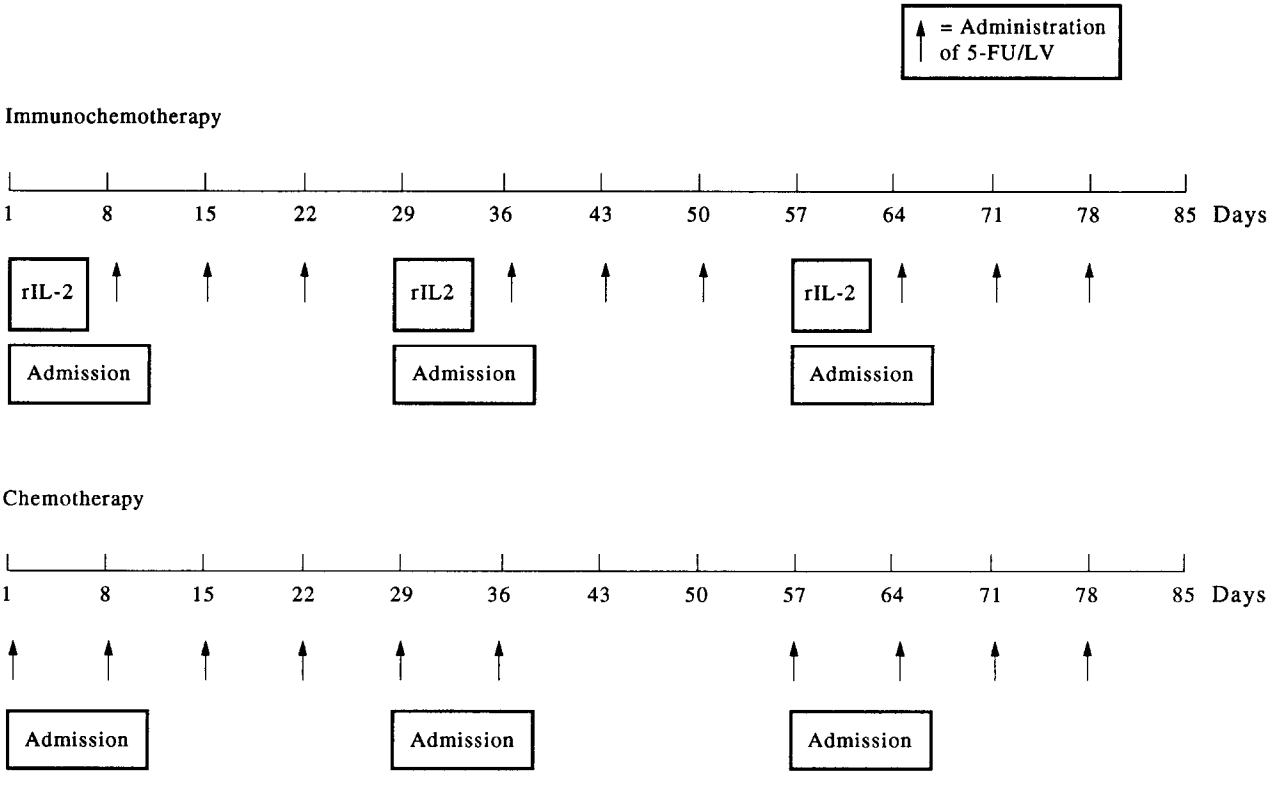

Figure 1. Trial design for the first 12 weeks of treatment.

Table 1. Time in trial and reasons for discontinuation

Patient no.	Days in trial	Complete 4-week block	Reason for withdrawal
Patients receiving immunochemotherapy			
1	112	4	Disease progression
2	85	3	Confusion on IL-2
3	155	5	Personal reason
4	71	2	Personal reason
5	84	3	Disease progression
6	28	1	Disease progression
7	28	1	Disease progression
8	28	1	Disease progression
9	28	1	Disease progression
Mean (S.D.)	68.7 (45.3)	2.3 (1.5)	
Median (range)	71.0 (28–155)	2.0 (1–5)	
Patients receiving chemotherapy			
10	56	2	Wished to withdraw
11	84	3	Side-effects
12	120	4	Disease progression
13	141	5	Personal reason
14	112	4	Disease progression
15	112	4	Disease progression
16	85	3	Trial completed
17	29	1	Treatment delayed
Mean (S.D.)	92.4 (36.5)	3.2 (1.3)	
Median (range)	98.5 (29–141)	3.5 (1–5)	

days 28–36 to keep constant the amount and timing of hospitalsisation and sleep deprivation.

Patients were discontinued from the trial if (a) their disease was progressing (judged by standard UICC criteria [5]), (b) a severe adverse event occurred or (c) treatment was delayed for 3 or more days (e.g. because of haematological abnormalities). Table 1 shows the number of days in the trial, the number of completed 4-week blocks, and the reason(s) for discontinuation for each patient. Patients receiving rIL-2 spent less time in the trial than the control patients (68.7 days and 92.4 days, respectively).

Assessments performed

Prior to recruitment, patients were screened using the SCID DSM-III^R [6], the Wechsler Adult Intelligence Scale [7] and the Mini Mental State Examination [8]. Various paper and pencil tests of mood, cognition, side-effects and treatment-related distress were administered weekly (except in the case of chemotherapy patients who were not assessed during weeks 7 and 8 of each cycle as they did not attend hospital at these times) (Walker and associates, manuscript in preparation).

Comprehensive cognitive assessment was carried out intensively using the Cognitive Drug Research System which has been shown to be a reliable, valid and sensitive measure of drug-induced changes in cognitive functioning [9–11]. The following tests were used in the assessment which took approximately 20 min to complete: Picture Recognition (ability to retrieve pictorial information from secondary memory), Word Recognition (cued ability to retrieve stored verbal information from secondary memory), Simple Reaction Time (speed of reaction to a single visual stimulus), Choice Reaction Time (a more complex measure requiring differential responding to two visual signals), Number Vigilance (sustained ability to concentrate) and Memory Scanning (ability to access short-term (working) memory).

Patients received four training trials prior to day 1; this has been shown to eliminate practice and training effects [12, 13]. Assessments were carried out at 10.30 hours (± 2 h) daily (including weekends) during admission to hospital and at weekly intervals (chemotherapy patients were not assessed at weeks 7 and 8). Patients were not allowed caffeine-containing drinks for 12 h prior to testing, and they were tested only when their temperature was normal. No hypnotics were given.

Patients

Inclusion criteria for the study were: locally advanced or metastatic colorectal cancer (Dukes' C or D), ambulatory performance status (Eastern Co-operative Oncology Group 0-1, Karnofsky > 80%), life expectancy of at least 3 months, no chemotherapy, radiotherapy or immunotherapy in the 4 weeks prior to recruitment, no evidence (radiological or clinical) of brain metastases or other neurological pathology, renal and liver function tests within normal limits (unless due to malignancy). The study was approved by the Joint Ethical Committee of the University of Aberdeen and Grampian Health Board. All patients gave signed, informed consent prior to participating in the study.

A total of 19 consecutive patients were randomised. However, one patient did not survive for the minimum period of 4 weeks and 1 withdrew in the first week as she objected to hourly blood pressure recordings at night. Data, therefore, were analysed for the 17 patients who completed a minimum of 4 weeks in the study. Nine received immunochemotherapy and 8 were given chemotherapy on its own.

During treatment, best responses were as follows. Of the patients receiving immunochemotherapy, 2 showed a complete response, 3 a partial response and 4 stable disease.

Table 2. Characteristics of groups at trial entry (means ± 1 SE)

	Immunochemotherapy ($n = 9$)	Chemotherapy ($n = 8$)
Age	59 (12) years	56 (10) years
Gender	5 males, 4 females	5 males, 3 females
Metastases		
Liver	4	4
Lymph nodes	2	2
Lymph nodes/lung	2	1
Liver/lung	1	0
Pelvis	0	1
HADS		
Anxiety score	4.6 (4.6)	5.1 (4.1)
Abnormal range	1	1
HADS		
Depression score	4.1 (2.2)	3.0 (2.7)
Abnormal range	0	0
WAIS		
Verbal IQ	116.9 (12.4)	110.6 (16.7)
Performance IQ	108.3 (5.6)	104.4 (10.9)
Full scale IQ	114.0 (9.4)	108.5 (14.0)

The comparable figures for the patients receiving chemotherapy were 2, 1 and 5, respectively. 6 patients receiving immunochemotherapy were withdrawn from the study because of disease progression and 3 patients in the chemotherapy group were withdrawn for this reason (Table 1). At the end of the study, 2 patients in both groups had had a complete response. 2 patients, both of whom received chemotherapy, were alive 4 years after treatment.

The patients were of above average intelligence (Full Scale IQ = 111, Verbal IQ = 113, Performance IQ = 106). None showed signs of dementia as assessed by the Mini Mental State Examination. The groups were well matched for age, gender, intelligence, anxiety and depression (Table 2). At trial entry, 4 patients met DSM-III^R criteria for a psychiatric disorder (3 patients who had received immunochemotherapy—1 major depression, 1 adjustment reaction (depression) and social phobia, and 1 social phobia; and 1 patient who had received chemotherapy—adjustment reaction (depression)).

RESULTS

Figures 2–4 shows baseline-corrected mean values (± 1 standard error) for the first 12 weeks of treatment for the two groups (thereafter, there were only 4 patients in each group).

Analyses of variance for repeated measures were carried out to evaluate changes in performance over time and differences within the 2 groups (SAS version 6.8, SAS Institute, Cary, North Carolina, U.S.A.). Immunochemotherapy produced impairment in the following cognitive functions as revealed by significant time × group interactions: simple reaction time ($F = 3.5$, df = 50, 532, $P = 0.0001$) and choice reaction time ($F = 1.6$, df = 50, 532, $P = 0.01$) (Figure 2), picture recognition sensitivity ($F = 1.9$, df = 50, 532, $P = 0.0003$) (Figure 3) and vigilance speed ($F = 1.7$, df = 50, 532, $P = 0.005$) (Figure 4). Although the overall analyses of variance for vigilance accuracy, memory scanning speed and picture recognition speed were not significant ($P > 0.05$, two-tailed), *t*-tests showed significant differences between the groups at various time points (see standard error bars in Figures 2–4). The general pattern observed was progressive deterioration in performance during, and immediately after, administration of rIL-2, followed by a return to baseline levels by day 15 of the cycle (10 days after the end of each infusion of rIL-2). Simple reaction time, however, did not return to baseline level until day 22 of each cycle. One patient became confused (see below) and, if she is excluded from the analysis, simple and choice reaction times show maximum deterioration on the last day of the 5 day infusion of rIL-2 or on the following day.

Compared with baseline, analyses of variance for patients who received chemotherapy on its own revealed significant impairment in simple reaction time ($F = 3.3$, df = 25, 151, $P < 0.001$), vigilance speed ($F = 2.2$, df = 25, 151, $P < 0.001$) and memory scanning speed ($F = 2.8$, df = 25, 151, $P < 0.0001$).

DISCUSSION

This study of the cognitive effects of rIL-2 infused continuously over 5 days (18×10^6 IU/m^2/24 h) has a number of desirable features including: (a) the use of a control group (chemotherapy only) to take into account the effects of sleep deprivation, diet, restricted mobility, concurrent chemotherapy and disease progression, (b) the use of highly sensitive, reliable, computerised tests performed daily during hospital admissions, and (c) rigorous discontinuation criteria.

Marked detrimental iatrogenic effects were brought about by the immunochemotherapy (Figures 2–4). The regimen of immunochemotherapy used in this study adversely affected response speed, vigilance and some aspects of memory. These deficits were reversible, at least for the group as a whole (one patient was withdrawn from the study because her cognitive functioning was clearly not returning to normal between cycles). For most patients, the maximum impairment occurred on the last day of infusion, or the day after, and this was followed by improvement on the succeeding days. The clinical implication of these findings is that, during infusions of rIL-2 in the doses used in this study, patients experience cognitive deficits which resemble some of the major cognitive impairments associated with dementias such as Alzheimer's disease [14]. Previous studies using non-computerised cognitive assessments also found

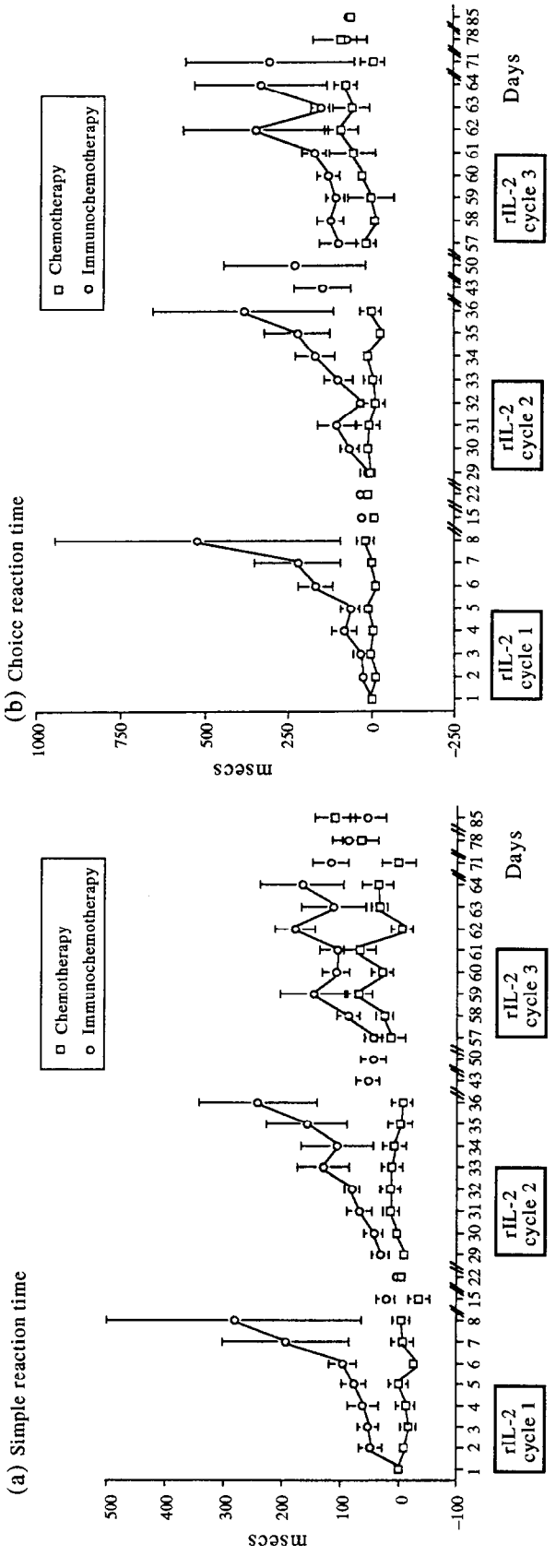

Figure 2. Reaction speed (baseline corrected means ± 1 SE).

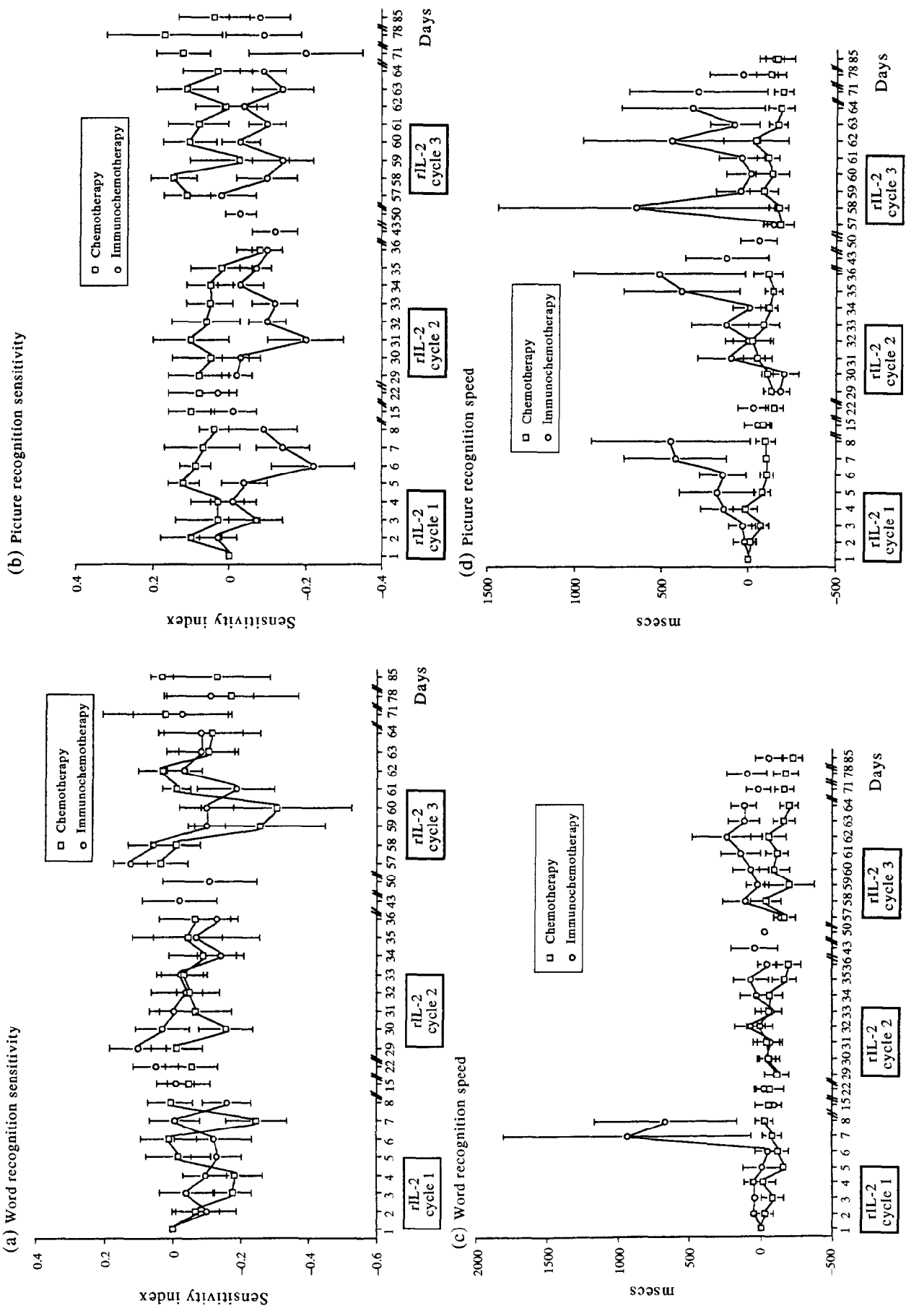

Figure 3. Word and picture recognition (baseline corrected means ± 1 SE).

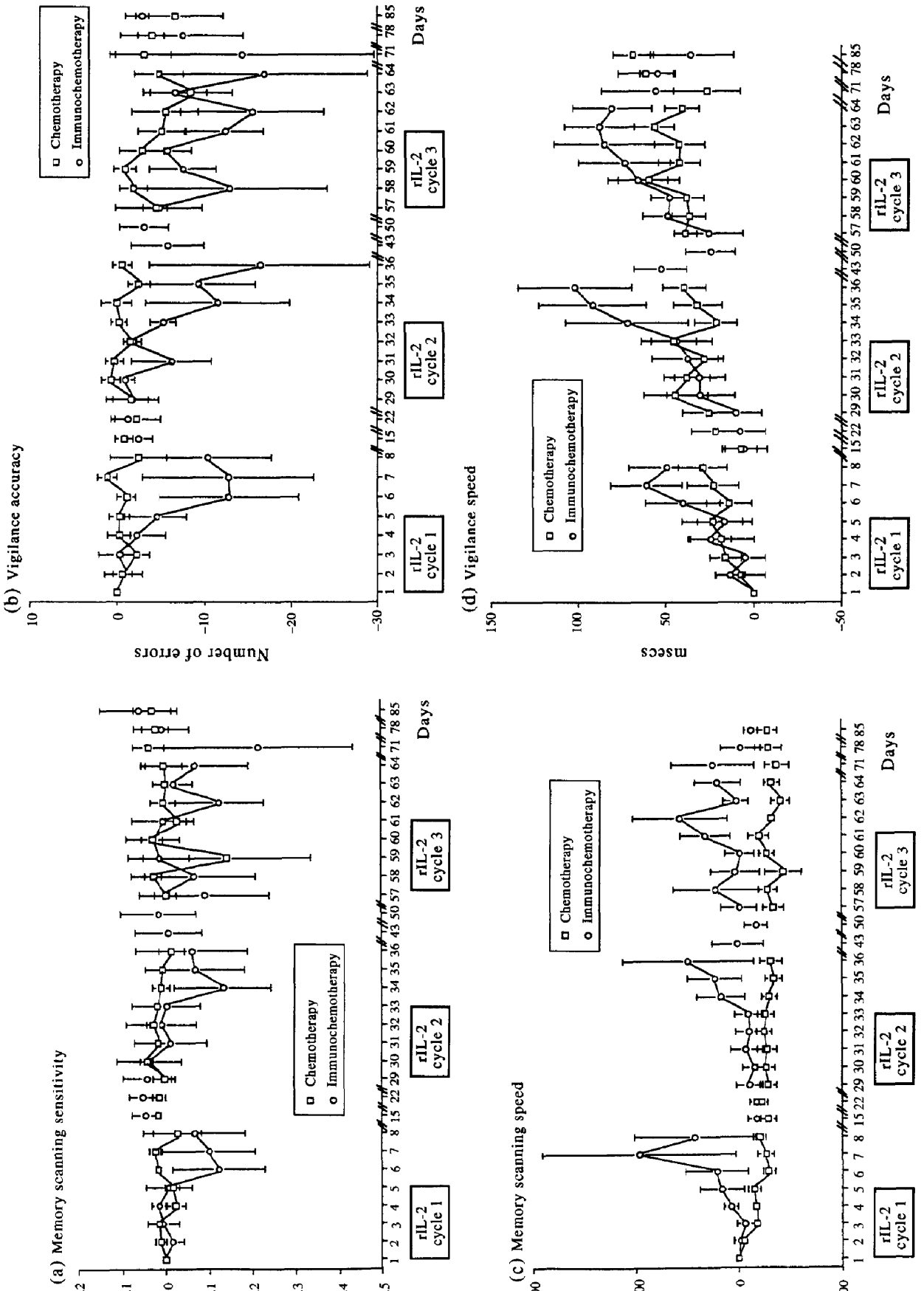

Figure 4. Memory scanning and vigilance (baseline corrected means ± 1 SE).

incidence of cognitive impairment [2, 3]. It is important to note that chemotherapy on its own was associated with significantly impaired simple reaction time, vigilance reaction time and memory scanning speed (the extra few days' hospitalisation to make the two groups comparable might have made a slight contribution to this). The cognitive effects of various common chemotherapeutic regimes clearly merit further study using state-of-the-art computerised assessment methods.

Two neuropsychiatric problems were observed during the trial. One patient repeatedly developed a hallucinatory syndrome. However, these severe effects were completely reversible within 48 h after the end of each infusion. (Interestingly, abdominal CT scans showed a complete response after three cycles of treatment; but the patient relapsed very rapidly following completion of treatment (6 cycles).) Another lady developed severe confusion and met the diagnostic criteria for delirium during all three infusions, even when she was given half the dose in cycle 3. She had been receiving morphine sulphate (MST) (up to 60 mg daily) for 8 weeks prior to the first infusion of rIL-2 because of liver pain and continued on morphine sulphate throughout treatment. The dose was increased to 90 mg daily on the first day of the first cycle of immunotherapy and it is possible, therefore, that this may have played a part in causing confusion. However, despite a reduction in the dose of MST (10–30 mg daily) during the second and third cycles, she again became confused which indicates that, during these cycles, the confusion was not a direct consequence of morphine sulphate. Immunochemotherapy was discontinued after the third cycle because of its psychological effects.

None of the patients were prescribed psychotropic medication whilst they were in the study. Apart from patient 17, who was taking diazepam 10 mg nocte as a hypnotic prior to trial entry, and continued throughout on this dose, no hypnotics were taken by any other patients in the study. Unlike Denicoff and associates [2] who administered major tranquilisers to 27% of their patients, we did not need to use this therapy in any of our cases.

There are several possible explanations for the effects observed in this study. One possibility is that the effects are a consequence of cerebral oedema [15] or the 'vascular leak syndrome' which is known to occur with rIL-2 therapy [16]. Psychological effects, therefore, may be due to fluid and electrolyte fluxes within different cerebral compartments. Investigations using positron emission tomography and magnetic resonance imaging could clarify this matter.

A second possibility is that the observations documented are caused by direct actions of rIL-2 on neuronal tissues. IL-2 receptors have been demonstrated on a variety of non-lymphoid cells [17] and astroglial cells. The latter are thought to be derived from the macrophage–monocyte cell lineage. There is now a substantial body of evidence suggesting a close interaction between the brain and the lymphoid compartment. Although no equivalent of theta antigen has been documented in human neurons, microglial cells possess some of the surface receptors found on circulating monocytes and tissue macrophages. Also, there is evidence for production of *in situ* cytokines (e.g. IL-2) and brain cell activation of cytokines (e.g. IL-1). These various mechanisms could account for the EEG abnormalities observed by Caraceni and associates [3] in patients receiving rIL-2 based therapy.

Finally, the psychological changes may be influenced by the neuroendocrine effects of rIL-2. Denicoff and associates [18] found that IL-2 treatment induced the release of neuroendocrine hormones, especially β-endorphin, ACTH and cortisol.

The feasibility of using the CDR computerised assessment system in hospital environments has been previously investigated. Baillie and associates [10] established that bedside operation of the tests was feasible as soon as 30 min after surgery in day-case patients. Moreover, Simpson and associates [14] demonstrated, in a hospital memory clinic, that normal elderly individuals (up to 94 years old) and demented patients (Mini Mental State Examination scores as low as 6 out of 30) could be assessed satisfactorily using the system. However, so far it has not been used with cancer patients. We had to discontinue testing on several occasions when one patient (2) was confused. However, apart from that, even in those patients with advanced disease, the Cognitive Drug Research system was a feasible and readily usable method for evaluating treatment-induced cognitive changes. It could usefully be included in quality of life assessments in clinical trials where sensitive and accurate treatment-related cognitive changes need to be carefully documented and critically evaluated.

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