

Neurotoxicity of Prophylactic Cranial Irradiation in Patients with Small Cell Carcinoma of the Lung

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Abstract—This study is concerned with effects of prophylactic cranial irradiation on neurological and mental functioning of patients with small cell cancer of the lung. Results are reported of a pilot study in two parts. In a prospective clinical-neurological study, 14 patients with small cell cancer of the lung were evaluated with standard neurological and bedside mental status examinations, before and after irradiation. Their performance was compared with evaluation results of seven small cell cancer of the lung patients who received no irradiation. Dysfunctions were exclusively found in the irradiated patients, which are interpreted as a contributory effect of prophylactic cranial irradiation. Results are reported of further neuropsychological investigation in a sample of five prophylactic cranial irradiation patients. The presence of a rather specific pattern of neuropsychic deficits was confirmed. Areas of malfunctioning were described with some clinical and research implications.

INTRODUCTION

NEWER treatment regimens in patients with small cell carcinoma of the lung (SCCL) have resulted in the prolongation of survival. With prolongation of survival related to effective combination of chemotherapy, brain metastases become more frequent [1, 2]. Its incidence may increase to 80% in patients with SCCL, who survive 2 years or more without prophylactic cranial irradiation (PCI) [3]. However, PCI has decreased the incidence of brain metastases [4] and therefore most current therapeutic regimens for patients with SCCL include PCI soon after the attainment of complete remission (CR), but it has not prolonged survival.

The irradiation of many patients who never develop brain metastases during life might only be tolerated if no noteworthy adverse effects are found. Since there are conflicting reports on acute and late effects in brain tissue from PCI [5-11], its use is not unanimously accepted as mandatory in SCCL. Because of the still uncertain adverse effects of PCI, these should be evaluated by neurological and neuro-psychological examinations in patients with SCCL who received PCI.

Our aim was to explore areas of neuro(psycho)-logical malfunctioning in patients with SCCL who received PCI. More specifically the purpose was to formulate trends and hypotheses, and select

methods to test them in a design devised to isolate the neuro(psycho)logical effects of PCI. Only such a study will allow a more definitive statement regarding the safety of PCI.

PATIENTS AND METHODS

Between June 1981 and December 1984, 33 patients with SCCL were treated according to a prospective protocol in which cyclophosphamide 1000 mg/m²/day, adriamycin 45 or 50 mg/m² and etoposide 100 mg/m² × 3 were given. The subjects, 28 males and five females, ranged in age from 42 to 76 years. A simple two-stage division is customarily employed in SCCL. Limited disease (LD) is confined to the hemi-thorax of origin, the mediastinum and supraclavicular nodes. In extensive disease (ED) tumor is found beyond these sites. In our study both LD and ED patients in complete remission received PCI, 30 Gy in 10 fractions in 2-3 weeks, concurrent with the fourth course of chemotherapy. Patients who did not achieve a response to chemotherapy did not receive prophylactic cranial irradiation. Seven of 33 patients, who developed central nervous system (CNS) metastases, were excluded from this study, the others had no evidence of tumor involvement of the CNS at any time during the course of their disease. In addition, five patients with other abnormal results on neurological examination before irradiation were not admitted to the study. Twenty-one patients, 17 males and four

females, ranging in age from 42 to 72 years, remained on study from 5 to more than 33 months (median of 14 months). For the purpose of the study patients were divided into four groups to the extent of the tumor dissemination and to whether they had undergone PCI. One group of 12 patients with LD had had PCI (group I). A second group of three patients with LD had never had PCI (group II). A third group of two patients with ED received PCI (group III) and a fourth group of four patients with ED had had no treatment of PCI (group IV). The controls (group II and IV) received chemotherapeutic agents similar to those from group I and III. To control for the possible effects of PCI, this group of seven patients with SCCL was similarly evaluated. Only patients who were awake and oriented for time, place and person have been examined. All patients were evaluated by clinical, neurological and bedside mental status examinations at the same time interval. Patients underwent follow-up examinations on a regular basis, initially before and after radiation therapy and subsequently every 3 months.

In some patients adverse effects of PCI were evaluated by computer tomography (CT) scan.

Further neuropsychological examination was performed in five subjects. These were selected from group I on no other criteria than availability at the time of the neuropsychological part of the study. All subjects were right-handed, four male, one female, average age was 61.8 years (range 54–70). All subjects had received PCI, average interval post PCI was 12.5 months (range 5–30). All subjects showed intact levels of consciousness and comprehension and were adequately oriented. All subjects were sufficiently motivated to cooperate and no intervening depressive, worrying or fatigue states were observed. Procedures consisted of: (i) interview for subjective complaints on a standard list of 42 items covering common areas of general physical, psychological and social sequelae of brain dysfunction of any etiology (results will be reported elsewhere); (ii) neuropsychological examination with standard and observational procedures to detect functional system abnormalities as mediated by cerebral structures along anterior–posterior and left–right dimensions and subcortical regions. For the present study a detailed discussion of these procedures is considered as not relevant. The complete “battery” includes 49 tests, subtests or methods. Several were omitted or replaced by others after the first trials. Among the qualitative observational procedures examination of limb and buccofacial dyspraxia, dynamic organization of hand motricity, thematic interpretation, routefinding (mazes) and various graphomotor constructional tasks are examples. Standardized intelligence testing (GIT), the Stroop color–word test, a visual

cancellation task, a standardized word learning experiment (15 word test), the Benton revised visual retention test and the Tokentest are examples of psychometric parts. For a comprehensive description of neuropsychological assessment and functional systems involved we refer to Lezak, Heilman *et al.* and Kolb *et al.* [12–16]. The duration of a complete examination varied from 2.5 to 5 hr. Two patients were re-examined after 1 year.

RESULTS

Results of neurological examinations

Table 1 presents the results of the neurological and routine bedside mental status examinations. Abnormalities were found in 12 patients. The most frequent problem encountered was loss of memory. This problem has been severe in six patients and has greatly impaired daily living activities. The remaining findings at neurological examinations at this stage were neuropathy, loss of hearing, somnolence, headache and dysarthria.

Three patients developed a syndrome characterized predominantly by somnolence followed by several days of anorexia and irritability. The symptoms appeared between 14 and 21 days after completion of radiation and lasted 10–15 days. In all cases of somnolence this complaint resolved spontaneously and completely. That the complaints are not a reflection of underlying CNS disease was indicated by mostly normal CT-scans.

Results of neuropsychological investigation

Table 2 summarizes the results of five patients in seven categories of neuropsychic functioning with clinical descriptive relevance. At this stage no attempts are made to further specify content or degree of each impairment, nor the pattern of dysfunctioning within each patient. All patients at first examination as well as the two re-examined showed deficits in the area of attentional and mental control processes. At least three, possibly four, patients performed below average on tasks for new verbal and visual learning, implying some degree of anterograde amnesia. Three patients at the first and another at the second examination manifested marginal or subnormal performances in the broad area of visual, perceptual, constructional and spatial abilities, some loss of fine motor control seems to be involved. The average IQ score for our sample was 110.6, range: 99–128, with no differences for the two patients re-examined. Actual IQ scores were comparable to estimated premorbid levels. No “significant” loss of general intellectual ability is implied. Qualitatively however in three patients there seemed to be some degree of disability in planning and goal directed routefinding which deserves further investigation. No clear orientation,

Table 1. Results of neurological and mental status examinations

	Group I LD + PCI	Group II LD - PCI	Group III ED + PCI	Group IV ED - PCI
Loss of memory	10/12	0/3	2/2	0/4
Neuropathy	7/12	1/3	2/2	1/4
Loss of hearing	3/12	0/3	2/2	0/4
Somnolence	3/12	0/3	0/2	0/4
Headache	3/12	0/3	1/2	0/4
Dysarthria	1/12	0/3	1/2	0/4

PCI: prophylactic cranial irradiation, LD: limited disease, ED: extensive disease.

Table 2. Summary of neuropsychological results

Function system category	Subnormal	
	first ex. (N : 5)	second ex. (N : 2)
1. Intellectual ability	0	0
2. Orientation		
time	0	0
place and topographic	0	0
person	0	0
3. Attentional and mental control processes	5	2
4. Mnesis		
verbal	3-4	1
visual	3-4	1
5. Phasis: aphasia tests	0	0
Related functions:		
fluency	1-2	1
reading speed	3	1
writing	2	1
arithmetic speed	3	1
6. Praxis		
buccofacial	0	0
upper limbs	0	0
7. Visuoperceptual, constructional and spatial abilities	3	2

dysphasic and dyspraxic errors were found. All patients e.g. performed normally on a standardized naming and the Tokenest. Loss of fluency, reading and arithmetic speed as shown in Table 2 might point to more specific language related disorders, an effect of mnesic and more general attentional, mental control and speed of information processing problems seems more plausible however.

Abnormalities in handwriting refer mainly to motor performance, and possible decrease of fine motor abilities, as mentioned before. Though not specifically tested for, no signs of agnosia, alexia or acalculia were observed.

Conclusion: all or most of the patients in our sample showed neuropsychic deficits which can be summarized as lying in the areas of attention and mental control, new learning, visual perceptual and in particular visuo-constructional abilities. Quali-

tatively a degree of goal directed planning difficulty, subtle, more general loss of speed of mental processing and loss of fine motor control is suggested in some patients. No patients presented with clear signs of general intellectual deterioration.

DISCUSSION

Most current therapeutic protocols for SCCL patients include PCI soon after complete remission with chemotherapy. There are, however, conflicting reports about neurological impairment in SCCL patients after PCI [5-11, 17-19]. Some studies have documented CNS damage in these patients, another shows occurrence of neurological impairment in patients who received chemotherapy only [20]. Contributing to these concerns are reports of cognitive deficits in children who received PCI and chemotherapy for acute leukemia [21].

Brereton *et al.* [11] described a syndrome including memory loss, tremor, dysarthria, slurred speech, somnolence and myoclonus in SCCL patients who received PCI and systemic chemotherapy. This syndrome began within 3 months after initiation of PCI and resolved after 3-6 months without apparent residual effects. Apart from these, we have found no other reports of neuro(psycho)logical evaluation with relevance for our population. For methodological reasons interpretation of our results is tentative. The outcome of bedside neurological and mental status evaluation shows that patients who had undergone PCI were more at risk of developing neurological and mental status abnormalities than those without PCI treatment. As all our patients had received chemotherapy, our data suggest an etiological role of PCI in the production of neurological dysfunction. No evidence of cerebral dysfunction was found in patients treated with chemotherapy only. Further neuropsychological examination reveals a rather specific pattern of neuropsychic deficits. These imply concomitants of cerebral dysfunction of a general nature, and no clear signs of focal impairment were found. As the results were obtained at an average post-PCI interval of 12.5 months and two patients were

re-examined after 1 year, at least some of these abnormalities may be longer lasting.

Contrary to expectation, interview and observation did not reveal significant worrying or depressive states. Also, the general somatic condition could not account to an important degree for deviant examination outcome. The data in this sample were exclusively obtained on patients in the PCI condition. No comparable data on patients with chemotherapy only were available. Therefore, isolation of PCI effects on neuropsychological outcome is not possible at this stage. Because SCCL patients receiving PCI seem to be at risk for incapacitating complaints and disruption of higher mental functions, clinical neuropsychological examination

as a matter of protocol may be indicated in this patient group. Tests and procedures to measure deficits in this group can be restricted to a relatively small "battery" of instruments. Neuropsychological data will be reported in more detail elsewhere. Considerations of sample size, comparable control group data, control for relevant variables (e.g. age, sex, time post-therapy, other neuropsychological etiologies, subjects' *a priori* knowledge of problems expected, order of test presentation) will be taken into account in a future design (in preparation).

Further prospective studies on mental status and neuropsychological deficits will be necessary to determine the rate of acute and chronic neurological toxicity caused by PCI.

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