Acta Oncologica Vol. 33, No. 2, pp. 159–164, 1994

LATE SEQUELAE IN CHILDREN TREATED FOR BRAIN TUMORS AND LUEKEMIA

BERTA JEREB, ROMAN KORENJAK, CIRIL KRŽIŠNIK, GABRIJELA PETRIČ-GRABNAR, LORNA ZADRAVEC-ZALETEL, JOŽICA ANŽIČ, JANEZ STARE

Forty-two survivors treated at an age of 2–16 years for brain tumors or leukemia were, 4–21 years after treatment, subjected to an extensive follow-up investigation, including physical examination and interview; 35 of them also had endocrinological and 33 psychological evaluation. Hormonal deficiencies were found in about two-thirds of patients and were most common in those treated for brain tumors. The great majority had verbal intelligence quotient (VIQ) within normal range. Also, the performance intelligence quotients (PIQ) were normal in most patients. However, the results suggested that the primary intellectual capacity in children treated for cancer was not being fully utilized, their PIQ being on the average higher than their VIQ; this tendency was especially pronounced in the leukemia patients.

Leukemias and brain tumors represent about 50% of childhood malignancies (1). With successful treatment the number of survivors is increasing (1–4), but the prolonged survival has been associated with long-term sequelae (5). Radiation therapy of the brain has been observed as one of the most common causes of late side effects. To which degree the severity of the brain damage is related to the radiation dose, to the concomitant chemotherapy or to the age of the patient (6–10), is uncertain. Some data indicate the influence of other factors that might be of importance (11–16).

We have studied late effects in 3 groups of patients who received irradiation of the brain. Group 1 consisted of leukaemias, group 2 of the brain tumors astrocytoma, germ cell tumor, and ependymoblastoma, and group 3 of medulloblastomas (which had received irradiation of the whole central nervous axis). The main aim of this study was to evaluate the psychosocial consequences of treatment. However, somatic changes and endocrinological deficiencies had to be asessed as well, in order to appreciate their possible influence on the emotional and mental state of the patients.

Received 7 October 1993.
Accepted 17 November 1993.
From the Institute of Oncology, Ljubljana (B. Jereb, G. Petrič-Grabnar, L. Zadravec-Zaletel), Clinical Center, Psychyatric outpatient department, Ljubljana (R. Korenjak), Clinical Center, Department of Paediatrics, Ljubljana (C. Kržišnik, J. Anžič), Institute of Biomedical Informatics Medical Faculty, Ljubljana (J. Stare), Slovenia.
Correspondence to: Berta Jereb, The Institute of Oncology, Zaloška 2, 61000 Ljubljana, Slovenia
Presented at the 18th International Congress of Chemotherapy Stockholm, Sweden, June 27–July 2, 1993.

Material and Methods

From 1971 through 1988, 878 patients with either leukemia or brain tumor, from 2 months to 16 years old, were admitted to the Oncological Institute for treatment. At the start of the study, 240 were more than 15 years old and had been observed for at least 4 years after treatment. These patients were invited for interview and evaluation, and 202 of them accepted the invitation. So far 42 patients treated for leukemia or brain tumor have been interviewed systematically according to the questionnaire, 35 have been endocrinologically evaluated and 33 have also undergone psychological testing. The 22 males and 20 females were between 2–16 (mean 8) years old at diagnosis, and between 15 and 26 (mean 18) years old at the time of evaluation. They had been followed from 4 to 21 years after treatment (median 11 years). There were 13 females and 6 males in the leukemia group, 4 females and 11 males in the 'astrocytoma' group, and 3 females and 5 males in the medulloblastoma group. (Table 1).

All patients in the 3 groups had received irradiation of the brain; 19 patients, treated for leukemia, had received whole brain radiation (24 Gy), as well as systemic chemotherapy (vincristine, prednisone, asparaginase, cyclophosphamide and intrathecal methotrexate). All had been hospitalized several times during treatment (5–10 times).

 ISSN 0284-186X

Table 1

Age at diagnosis. Number of patients (males/females)

Diagnosis	<5 yrs	5–10 yrs	>10 yrs	Total
Leukemia	10 (2/8)	6 (3/3)	3 (1/2)	19 (6/13)
Astrocytoma, etc.	3 (2/1)	5 (4/1)	7 (5/2)	15 (11/4)
Medulloblastoma	1 (1/0)	6 (3/3)	1 (1/0)	8 (5/3)
Total	14 (5/9)	17 (10/7)	11 (7/4)	42 (22/20)

Fifteen patients with either astrocytoma (n = 12), ependymoblastoma (n = 1) or germ cell tumor (n = 2) had been operated, (total removal in 4, subtotal removal in 11) and had radiation therapy to the tumor bed (30–55 Gy). They had been hospitalized once or twice for treatment. Of the 8 patients with medulloblastoma, 4 had been operated with total removal of the tumor and 4 with subtotal removal. All had got radiation therapy to the whole central nervous axis (36 Gy) with a boost to the posterior fossa bringing the total dose up to 55 Gy. During treatment they were hospitalized once or twice.

At the interview, the following aspects were investigated; awareness and experience of past treatment, experience of fear at the time of treatment, present way of life, including schooling, relationships within family, marital status, social life, adjustment to environment, education, profession, jobs, religion, use of free time, and plans for the future.

All patients underwent general physical examination. Height, weight and clinical abnormalities were recorded as were Tanner stages of pubic hair, genital development, and onset and course of puberty.

Endocrine assessment. Thyroid status was assessed by measurement of the serum concentration of T4, T3 (RIA method, SPAC, Mallincrot) and TSH (DELFIA.LKB) in basal state and 30 min after stimulation with 100 μg TRH. At the same time basal and stimulated levels of prolactin (DELFIA-LKB) were analyzed. Stimulation test for evaluation of growth hormone (RIA-GH, Pharmacia) consisted of L-DOPA (250 mg orally when body weight was $\leq$30 kg, 500 mg when >30 kg) and propranolol (0.75 mg per kg up to a maximal dose of 40 mg). GH was measured 60 and 90 min after the onset of sleep. Growth hormone deficiency was defined as GH level <10 μg/l after stimulation. In some patients only Somatomedin-C values were determined by the IRMA-IGF-I, DSL method. Testosterone (RIA, IMUNOTECH), and estradiol (DELFIA-LKB) levels were measured in the basal state. Concentrations of LH and FSH (DELFIA-LKB) were determined before, and 10, 20, 30, 60 min after i.v. administration of 100 μg GnRH.

Psychological evaluation. The clinical psychologist performed the evaluation without detailed information about the patient, not to be influenced by the clinical data. The psychosocial testing included the Bender visual Motor Gestalt Test, the Wechsler Bellevue Intelligence Test and the Rorschach Personality Test. With these tests we tried to elucidate the presence and extent of possible psycho-organic sequelae of the cancer treatment. Rorschach Personality Test was meant to show possible emotional deviations attributable to the experience of having undergone diagnosis and treatment of a malignant disease. Psycho-organic changes could emerge as a consequence of anatomical changes due to the disease and/or the treatment. These are defined as a general psycho-organic syndrome, expressed through different kinds of cerebral dysfunction, mainly of visual-motoric co-ordination, of memory function, of concentration, of attention and flexibility of thinking, and of instability of emotions. These changes were also tested by the Rorschach test establishing the emotional mode and its changes, the sociability and the whole spectrum of the patient's sphere of interest. We have assessed the presence of different signs and, on the basis of general psychological criteria, the level of psycho-organic damage and emotional disturbance. With the Wechsler-Bellevue intelligence test we tried to evaluate mental deterioration. This means the decline of mental ability in excess of the decline which is a consequence of age f.i. It is a pathological event conditioned by organic brain damage.

Results

To the first interview all except 2 patients appeared, accompanied by their mother or by both parents, (2 came with their partners). Those who appeared with their parents rarely answered the first question by themselves, but did so after encouragement. The general impression of shyness remained throughout the interview. They were willing to undergo the testing, which was, however, often delayed in order not to collide with schooling or work. The majority remembered treatment as unpleasant. Eight patients had been too young at the time of treatment to remember. The most unpleasant experience remembered was the intrathecal treatment and next came the intravenous chemotherapy, but not radiation therapy. Hospitalization had been experienced as very depressing in the beginning but in the majority of patients this impression had changed and after some time they had found the hospital personal nice and a few had even been unhappy to leave the hospital. The 4 patients who described the treatment as pleasant found it interesting with many new friends and a different environment (Table 2). Fourteen patients stated to have experienced fear, mainly from injections and pain.

Sixteen patients said that they were informed about the nature of their disease during treatment. Only in a few cases this information derived from their mothers, others received it from the nurses or, rarely, from doctors. Fifteen patients read about it when they were older. Eleven patients received the information about their past condition at the time of the present evaluation only, when they were also told why the evaluation was desirable.

Table 2

Reminiscence of treatment and obvious treatment sequelae. Number of patients

	Leukemia	Astrocytoma, etc.	Medulloblastoma	Total
Reminiscence of treatment				
Does not remember	3	5	0	8
Pleasant	2	1	1	4
Unpleasant	6	8	4	18
Very unpleasant	8	1	3	12
Obvious sequelae				
None	13	5	1	19
Slight	3	6	4	13
Moderate	1	1	2	4
Severe	0	2	1	3
Secondary tumor	2	1	0	3
Total number	19	15	8	42

Table 3

Short Stature. Number of patients

	Leukemia	Astrocytoma, etc.	Medulloblastoma	Total
No	11	9	4	24
Yes	3	4	3*	10
Total	14	13	7*	34

* = one dwarf

Severe somatic sequelae were observed in 3 patients treated for brain tumor: blindness in one, severe adiposity (thalamic syndrome) in a second patient and pituitary dwarfism in the third. Three patients developed secondary tumors. One girl had osteogenic sarcoma of the mandible diagnosed 7 years after treatment for leukemia and another girl had a non-Hodgkin's lymphoma diagnosed 5 years years after treatment for leukemia. They are both alive and well 8 and 15 years from treatment for their secondary tumors. One patient with astrocytoma died from glioblastoma diagnosed 20 years after treatment for his first tumor. Patients with light or moderate changes in physical appearence had microcephaly or were short of stature (below 3th percentiles from the normal range) (Table 3).

Of the 35 endocrinologically evaluated patients 24 had hormonal deficiencies. This was observed more often in patients with brain tumors than in those with leukemia. Hypogonadismus and impaired growth hormone secretion were the only pathological findings in 8 patients (4 of each deficiency) out of the 14 treated for leukemia. None of the evaluated patients had diabetes insipidus or adrenal gland deficiency (Table 4).

The great majority of patients in all 3 groups had verbal intelligence quotient (VIQ) values within normal range and there were no obvious differences between the 3 groups. (Table 5). The performance intelligence quotient (PIQ) values in the leukemia group, however, was for all 14 patients within normal or above normal range. In this repsect there seemed to be a difference between the leukemia group and the brain tumor group (Table 5). Emotional disorder and psychoorganic syndrom were rather evenly distributed between the 3 groups (Table 6).

Table 4

Endocrinological deficiencies. Number of patients

	Leukemia	Astrocytoma, etc.	Medulloblastoma	Total
None	6	2	3	11
Hypothyreosis	0	0	0	0
Hypogonadism	4	0	2	6
GH deficit	4	3	1	8
Hypothyreosis + hypogonadism	0	1	0	1
Hypothyreosis + GH deficit	0	1	1	2
Hypogonadism + GH deficit	0	3	0	3
Hypothyreosis + hypogonadism + GH deficit	0	3	1	4
Total number with deficiency	8	11	5	24
Total number of patients	14	13	8	35

Table 5

Verbal and performance IQ. Number of patients

	Leukemia	Astrocytoma, etc.	Medulloblastoma	Total
Verbal IQ				
<80	3	3	2	8
80–100	10	8	4	22
>100	1	1	1	3
Performance IQ				
<80	0	3	3	6
80–100	10	8	2	20
>100	4	1	2	7
Total number of patients	14	12	7	33

Table 6

Emotional disorders and psycho-oraganic syndrome. Number of patients

	Leukemia	Astrocytoma, etc.	Medulloblastoma	Total
Emotional disorders				
None	1	4	0	5
Slight	8	4	5	17
Significant	5	4	1	10
Very significant	0	0	1	1
Psycho-organic syndrome				
None	5	1	1	7
Slight	4	0	0	4
Significant	2	5	4	11
Very significant	3	4	2	9
Epilepsy	0	2	0	2
Total number	14	12	7	33

All patients were attending, or had been graduated from, some school, 3 had auxiliary schooling, and 2 from the astrocytoma group were university graduates. Patients with brain tumors seemed to perform worse professionally. All 5 patients not at work (3 on disability pension) had brain tumors.

Over one half of the patients regarded their social life as rewarding (Table 7). Thirty-five (83%) of the 42 patients declared themselves religious, and 28 (75%) of these actively so. In our general population these percentages are 70% and 10% respectively. Eleven patients were parents and had a total of 14 children; 9 of these children derived from leukemia parents. No parent had more than 2 children.

Table 7

Social life. Number of patients

	Leukemia	Astrocytoma etc.	Medulloblastoma	Total
None	0	1	1	2
Poor	8	7	3	18
Rich	11	7	4	22
Total	19	15	8	42

Discussion

Even if the number of our patients is low, some trends can be discerned on the basis of our study. Three patients treated for leukemia had VIQ below 80 but substantially higher PIQ, putting them within the range for normal intelligence. Since PIQ reflects mainly inborn intellectual capacity, the patients' functional setbacks may be more likely due to emotional disturbances. A similar tendency was seen in patients with PIQ above 110: only one of these scored similarly high VIQ, giving support to our hypothesis that in patients treated for leukemia, emotional disturbance affects cognitive function negatively by denying the patient the full use of his (her) inborn intellectual capacity.

There were more brain tumor than leukemia patients with VIQ below 80 and they also scored lower on PIQ. This may be due to brain damage caused by tumor and surgery (18). Evidence of psycho-organic syndrome could support this. The syndrome was more severe in patients treated for brain tumors than in those treated for leukemia. It was evaluated in terms of poor visual-motoric coordination, disturbance of thinking, low attention and concentration, defective memory and rigidity of thinking. The psycho-organic syndrome was frequent also in pa-

tients with leukemia, but tended to be less severe. We suppose that the syndrome was mainly the consequence of surgery and radiation treatment, probably in association with chemotherapy (19). The degree of mental deterioration was generally lower (16–25%) in patients treated for leukemia than in patients with brain tumors (26–35%), which could be in agreement with the supposed etiology. The suspicion that younger children may be more susceptible to brain damage due to radiation and/or chemotherapy could not be confirmed in our study (19–21).

Emotional disturbance was evaluated mainly in terms of emotional instability, personal immaturity, poor control of emotional reactions, inner insecurity, proneness to despondency, need for human relations and consequent difficulty in communication. The Rorschach test showed emotional disturbance to some degree in almost all our patients, equally distributed among the groups. This high incidence could be expected from the frequency of the psychoorganic syndrome, which was often accompanied by emotional disturbance. The high incidence of emotional disturbance in children with leukemia may be explained by their frequent hospitalization before the age of 5 years, experiencing this trauma during the most decisive phases of their development. During this time the structured personality emerges with far reaching consequences for the future life pattern (22–24).

The role of chemotherapy has been mentioned in connection with organic changes. It is likely that chemotherapy affects emotions even more by influencing the development of the personality during the treatment (24–26) with consequences later on.

A third, but not the least important, factor in the development of emotional disturbance seems to be frequent and repeated hospitalizations of the leukemia patients with concomittant variations in their state of health, surely contributing to emotional insecurity and anxiety. Clearly, emotional disturbance in a small child develops in an interplay with his (her) parents, other family members as well as the medical personel.

An additional burden, not investigated here, is the social prejudice which some of them meet. An example of this is a female patient in our group, who had abdominal irradiation for her secondary tumor, followed by infertility, and who, as a grown-up married woman, was denied adoption on the grounds of her being a cancer patient.

ACKNOWLEDGEMENT

This work has been supported by a grant No. P3-5249-302 from Ministry of Science and Technology of the Republic Slovenia.

REFERENCES

1. Cancer incidence in Slovenia 1987. Ljubljana: Institute of Oncology, Cancer Registry of Slovenia, 1991.
2. Bleyer WA. The impact ot childhood cancer on the United States and the world. Cancer 1990; 40: 355–67.
3. Hammond GD. The cure of childhood cancers. Cancer 1986; 58: 407–13.
4. Hawkins MM. Long term survival and cure after childhood cancer. Arch Dis Child 1989; 64: 798–807.
5. Green DM, D'Angio GJ, eds. Late effects of treatment for childhood cancer. Current Clinical Oncology. New York: Wiley-Liss, 1992.
6. Packer RJ, Meadows AT, Rorke LB, Goldwein JL, D'Angio G. Long-Term sequelae of cancer treatment on the central nervous system in childhood. Med Pediatr Oncol 1987; 15: 241–53.
7. Mostow EN, Byrne J, Connelly RR, Mulvihill JJ. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. J Clin Oncol 1991; 9: 592–9.
8. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumours. N Engl J Med 1993; 328: 87–94.
9. Brouwers P, Poplack D. Memory and learning sequelae in long-term survivors of acute lymphoblastic leukemia: association with attention deficits. Am J Pediatr Hematol Oncol 1990; 12: 174–81.
10. Halberg FE, Kramer JH, Moore IM, Wara WM, Matthay KK, Ablin AR. Prophylactic cranial irradiation dose effects on late cognitive function in children treated for acute lymphoblastic leukemia. Int J Radiat Oncol Biol Phys 1991; 22: 13–6.
11. Eiser C. Intellectual abilities among survivors of childhood leukemia as a function of CNS irradiation. Arch Dis Child 1978; 53: 391–5.
12. Meadows AT, Massari DJ, Fergusson J, Gordon J, Littman P, Moss K. Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukemia treated with cranial irradiation. Lancet 1981; 2: 1015–8.
13. Peckham VC, Meadows AT, Bartel N, Marerro O. Educational late effects in long-term survivors of childhood acute lymphocytic leukemia. Pediatrics 1988; 81: 127–33.
14. Eiser C, Lansdown R. Retrospective study of intellectual development in children treated for acute lymphoblastic leukaemia. Arch Dis Child 1977; 52: 525–9.
15. Tamaroff M, Salwen R, Miller DR, Murphy ML, Nir Y. Neurophysiologic sequelae in irradiated (1800 rads (r) 2400 r) and non-irradiated children with acute lymphoblastic leukemia (all). Proc ASCO 1985; 4: 165.
16. Mulhern RK, Wassserman AL, Fairclough D, Ochs J. Memory function in disease-free survivors of childhood acute lymphocytic leukemia given CNS prophylaxis with or without 1 800 cGy cranial irradiation. J Clin Oncol 1988; 6: 315–20.
17. Bamford FN, Jones M, Pearson D, Ribeiro GG, Chalet SM, Beardwell CG. Residual disabilities in children treated for intracranial space-occupying lesions. Cancer 1976; 37: 1149–51.
18. Fogarty K, Volonino V, Caul J, et al. Learning disabilities following CNS irradiation. Clin Pediatr 1988; 27: 524–8.
19. Chessells JM, Cox TCS, Kendall B, Cavanagh NPC, Jannoun L, Richards S. Neurotoxicity in lymphoblastic leukemia: comparison of oral and intramuscular methotrexate and two doses of radiation. Arch Dis Child 1990; 65: 416–22.
20. Lannering B, Marky I, Lundberg A, Olsson E. Long-term sequelae after pediatric brain tumors: their effect on disability and quality of life. Med Pediatr Oncol 1990; 18: 309–10.
21. LeBaron S, Zeltzer PM, Zeltzer LK, Scott SE, Marlin AE. Assessment of quality of survival in children with medulloblastoma and cerebellar astrocytoma. Cancer 1988; 62: 1215–22.

22. Suc E, Kalifa C, Brauner R, et al. Brain tumours under the age of three: the price of survival. Acta Neurochir 1990; 106: 93–8.
23. Waber DP, Urion DK, Tarbell NJ, Niemeyer C, Gelber R, Sallan SE. Late effects of central nervous system treatment of acute lymphoblastic leukemia in childhood are sex-dependent. Dev Med Child Neurol 1990; 32: 238–48.
24. Eiser C. Cognitive deficits in children treated for leukaemia. Arch Dis Child 1991; 66: 164–8.
25. Ell K, Nishimoto R, Morvay T, Mantzell J. Hamovitch M. A longitudinal analysis of psychological adaptation among survivors of cancer. Cancer 1989; 63: 406–13.
26. Love RR, Leventhal H, Easterling DV, Nerenz DR. Side effects and emotional distress during cancer chemotherapy. Cancer 1989; 63: 604–12.