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Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years

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Abstract Intensive multimodality treatment has led to a remarkable improvement of prognosis in paediatric cancer patients, however, a great number of long-term survivors suffer from considerable tumour- or treatment-related late effects. Between January 1990 and December 1998, 223 consecutive survivors of childhood malignancies entered a prospective follow-up study designed to evaluate the frequency and severity of tumour- and/or therapy-related long-term sequelae. After cessation of therapy and subsequently once a year, all patients underwent a detailed examination programme including physical examination, laboratory tests, abdominal sonography, echocardiography, electrocardiography, electroencephalography, spirometry, audiometry, ophthalmological examination and endocrine stimulation tests. Median follow-up was 5 years (range 0.4 to 9.6 years). A total of 167 patients (75%) had at least one chronic medical problem of whom 80 needed permanent medical support. The organ systems most frequently affected were the nervous system in 39%, the endocrine system in 32%, the ears/eyes in 22%, the kidneys in 17%, and the liver in 12% of the patients. Some late effects (endocrine deficits, hearing loss, tubulopathy) were primarily diagnosed only several years after the end of oncological therapy.

Conclusion The results of this study indicate that a considerable number of former paediatric cancer patients suffer from remarkable long-term side-effects. Since life quality is an important parameter of cancer survival, careful follow-up of long-term survivors is mandatory with the aim to reduce or even abrogate possible side-effects at the earliest time.

Key words Long-term late effects · Childhood · Cancer · Therapy · Follow-up examinations

Abbreviations CBC complete blood count · CIS cisplatin · CP cyclophosphamide · ECHO echocardiography · GH growth hormone · HBV hepatitis B virus · HC hepatitis C virus · IFO ifosfamide · MCD median cumulative dosage · NCI National Cancer Institute

Introduction

Advances in the treatment of paediatric malignancies have led to dramatically improved long-term survival rates. Currently it can be expected that about 70% of all childhood cancer patients will be cured of their disease [54]. The increased number of survivors has therefore shifted the attention to the possible long-term conse-
quences of anti-neoplastic therapy. Surgery, radiation, and chemotherapy as well as the underlying disease may cause late-appearing damage to different organ systems, resulting in serious morbidity with alteration of quality of life. Most frequent side-effects are endocrine dysfunctions, neurological deficits, cardiopulmonary failure, impairment of hepatic, renal and visual functions and hearing loss [22, 23, 25, 29, 32, 33, 46, 49]. Up to now the late effects of treatment in paediatric malignancies were mostly analysed retrospectively [27, 48, 53]; in contrast the present study was intended to evaluate the frequency and severity of therapy- and/or tumour-related late effects in 223 consecutively treated childhood cancer patients prospectively in order to detect and counteract possible disabilities at the earliest time.

Patients and methods

Patients

From January 1990 to December 1998, 454 children and young adults with different malignancies were admitted to the Division of Paediatric Haematology and Oncology, Department of Paediatrics, Graz, Austria. 336 are alive with 93 still receiving anti-neoplastic therapy. A total of 243 patients have finished oncological therapy of whom 20 are lost to follow-up or followed-up by another institution. The remaining 223 consecutive, long-term survivors (121 males, 102 females) are the subjects of the present study. Median age at diagnosis was 7.2 years (range 0.1–27.8 years) and median age at cessation of therapy was 8.1 years (range 8.0–29.1 years). Median duration of follow-up is currently 5 years (range 0.4–9.6 years). Some 54 patients had a brain tumour, 50 leukaemia, 34 lymphoma, 23 neuroblastoma, 14 bone sarcoma, 12 nephroblastoma, 12 soft tissue sarcoma, 11 germ cell tumour, four Langerhans cell histiocytosis, five liver tumour, three retinoblastoma, and one thyroid carcinoma. Of the 223 study patients, 182 (81.6%) were treated according to the current multicentre treatment protocols used in Germany and Austria. A group of 41 (18.4%) patients were treated out of a special study protocol. Most of these 41 patients had localised tumours (e.g. cerebellar astrocytoma, nephroblas
toma or neuroblastoma I) and were treated by tumour resection only. 41/223 patients were treated by surgery alone and 28/223 patients by chemotherapy alone, whereas most patients (n = 154) received at least two different treatment modalities (chemotherapy and/or radiation therapy and/or surgery). The most frequently used study protocols were as follows: Berlin-Frankfurt-Münster (BFM) study group (ALL-BFM 86/90/95, ALL-BFM-REZ 87/90, AML-BFM 93, NHL-BFM 86/90/95) (n = 66), German/Austrian paediatric brain tumour study group trial HIT 89/91 (n = 18), Hodgkin disease protocols (DAL-HD 90, HD 95) (n = 16), Austrian neuroblastoma protocol A-NB-94 (n = 14), co-operative soft tissue sarcoma studies (CWS 86/91/96) (n = 12), Wilms tumour studies (Austrian/Hungarian Wilms tumour study 89, SIOP-93-01/ GPOH) (n = 12), co-operative Ewing sarcoma studies (CESS 86, EICESS 92) (n = 9), co-operative osteosarcoma studies (COSS 86, 91/96) (n = 7). Some 28 patients were treated according to other protocols.

Pre-treatment investigations

All our patients underwent pretherapeutically a standardised laboratory investigation including complete blood count (CBC), serum parameters (electrolytes, liver enzymes, bilirubin, cholesterol, creatinine, BUN, glucose, lactate dehydrogenase, alkaline phosphatase), coagulation tests, and urine analysis (creatinine clearance, tubular phosphate reabsorption rate, fractionated excretion rate of sodium and potassium). In most patients serological testing for viral antibody titres (hepatitis A virus, hepatitis B virus (HBV), varicella zoster virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus), chest X-ray, and abdominal sonography were performed before initiation of treatment. 2-Dimensional echocardiography (ECHO) and ECG were initially done in cases of planned anthracycline administration; EEG was done in selected brain tumour patients. Pre-treatment hepatitis C virus (HCV) antibody testing was introduced for all patients after 1993.

Examinations after completion of therapy

After completion of therapy all 223 patients underwent a detailed examination programme including careful physical examination, assessment of height, weight, height velocity and pubertal status according to the guidelines of Tanner and Whitehouse [50], CBC, analysis of serum parameters, urine analysis, screening for viral infections (hepatitis A, HBV, HCV, varicella zoster, cytomegalovirus, herpes simplex, Epstein-Barr virus), and testing for immunisation titres (antibodies to tetanus, diphtheria, Haemophilus type b, poliovirus and central European encephalitis virus, measles, mumps and rubella virus). Chest X-ray, abdominal sonography, brain CT scan, 2-dimensional ECHO, ECG, EEG, spirometry, audiometry and ophthalmological examination were performed additionally. All patients with clinical signs of endocrine dysfunction and all patients after cranial irradiation underwent a combined stimulation test of the anterior pituitary function as described [40]. In addition determination of serum basal TSH, FT4, and FT3 was performed in all patients after mediastinal, cervical, and cranial irradiation. Neuropsychological testing was not performed in the present study, but is the subject of a subsequent ongoing study.

Yearly examinations

At yearly intervals all patients underwent a clinical examination including assessment of height, weight, height velocity and pubertal status, CBC, examination of serum parameters and urine analysis as described above. In addition, ECG and ECHO (in the case of previous anthracycline therapy or mediastinal irradiation), measurement of basal TSH, FT4 and FT3 (in the case of irradiation of the thyroid region), abdominal sonography, spirometry and audiometry were performed every other year.

Organisational and economic aspects

All follow-up examinations were performed in the outpatient clinic of the Division of Paediatric Haematology and Oncology. The patients were informed about the planned procedure of follow-up at the end of the oncological therapy. During the first follow-up visit and subsequently from visit to visit the dates for further examinations were fixed. The costs for all services required were covered by the Austrian health insurance companies.

Chronic medical problems and degree of disability

Similar to the definition of Stevens et al. [48], chronic medical problems were defined as those pathological findings which were thought to justify ongoing medical intervention and/or causing, or were likely to cause, functional difficulty or disability. The common toxicity criteria adopted by the National Cancer Institute (NCI) and/or the need of permanent therapeutic interventions formed the basis to distinguish clinically relevant late effects from mild disabilities [9]. According to these criteria, late effects were categorised