Late effects of cancer treatment. Studies in children and young adults

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Summary

This thesis deals with the topic of iatrogenic late effects of childhood and adolescent cancer treatment. Although the treatment of children and adolescents with cancer has been increasingly successful over the last few decades, the aggressive treatment modalities needed to achieve this improvement may produce adverse late effects that interfere with quality of life or even may be life-threatening. The pattern of late effects includes a variety of mild and severe morbidity.

Chapter 1 gives a general overview of late effects which are determined by the interplay of disease, patient and treatment. Of these, treatment generally has the greatest impact.

The next three chapters deal with anthracycline-related cardiac damage, which can be one of the most devastating and potential life-threatening late effects of cancer treatment.

In the study described in **chapter 2**, we assessed cardiac function in long-term survivors of malignant bone tumors who were treated according to Rosen's T5 or T10 protocol, both including doxorubicin. Thirty-one patients, median age at diagnosis 17.8 years (range 10-45) were evaluated 8.9 years (range 2.3-14.1) following completion of treatment. Cumulative dose of doxorubicin was 360 mg/m^2 (range 225-550). The evaluation consisted of a history, physical examination, electrocardiogram (ECG), signal averaged ECG, 24-hr ambulatory ECG, echocardiography and radionuclide angiography. Eighteen of 31 (58%) patients showed cardiac toxicity, defined as having one or more of the following abnormalities: late potentials, complex ventricular arrhythmias, left ventricular dilatation, decreased shortening fraction, or decreased ejection fraction. The incidence of cardiac abnormalities increased with length of follow-up ($p \leq .05$). We found no

correlation between cumulative dose of doxorubicin and cardiac status, except for heart rate variability (HRV). These findings suggest that HRV could be a sensitive indicator of cardiotoxicity.

The same patient group was re-evaluated 5 years later **(chapter 3)**. Twenty-nine of the 31 patients participated; median follow-up was 14.1 years (range 7-18.7). Median age at the time of the study was 32.5 years (range 19.7-52). The evaluation consisted of an ECG, 24-hr ambulatory ECG with analysis of HRV and echocardiography. We found no progression of ECG abnormalities, arrhythmias or echocardiographic abnormalities. Females were at risk of reduced contractility (p=.006). HRV was significantly reduced compared to age- and sex matched controls and compared to the previous results. Again HRV appeared to be a highly sensitive test of cardiotoxicity.

One of the well-known risk factors of anthracycline-induced cardiotoxicity is cumulative dose. Therefore we tried to identify a lower threshold dose of daunorubicin (DNR) which could be considered to be safe with regard to cardiac damage **(chapter 4)**. Cardiac function was assessed in 90 event-free survivors of childhood acute lymphoblastic leukemia (ALL) 14.8 years (range 11.4-17.8) years after treatment according to the Dutch Childhood Leukemia Study Group protocol ALL V. In this protocol patients were randomized to receive (group B) or not to receive (group A) DNR 25 mg/m^2/week i.v. during the first 4 weeks of induction treatment. Median age at diagnosis was 4.5 years (range 1.2-14.9). The cardiac evaluation consisted of a history, physical examination, ECG, 24-hr ambulatory ECG, and echocardiography. Electrocardiographic data, HRV, left ventricular contractility, wall stress, and diastolic function were within normal limits. No difference could be shown between data from group A (n=40) and group B (n=50). We concluded that DNR 100 mg/m^2 given in 4 doses of 25 mg/m^2/week appeared to be a safe dose in induction treatment of ALL.

Chapter 5 deals with the topic of psychosocial adjustment of bone tumor patients following limb salvage or amputation. In 33 long-term survivors of lower extremity bone cancer quality-of-life data were studied following limb salvage compared to amputation. Self-report questionnaires, semistructured interviews and visual analog scales were used to measure psychoneurotic and somatical distress, activities of daily living, self-esteem, and adjustment to illness. Fourteen patients with limb salvage, median age 24 years (range 13-56), and 19 amputees, median age 27 years (range 21-53), were evaluated 10 years (range 2-17) after surgery. The differences between the two groups were not statistically different. However, physical complaints were reported more often by limb salvage patients, whereas the amputees showed a trend toward lower self-esteem and isolation in social life, due to their disability. Both groups had equal scores for quality of life and disability as measured on the visual analog scale. These findings could support the cosmetic advantage of limb salvage compared to amputation.

In **chapter 6** a study on incomplete regrowth of scalp hair after chemotherapy-induced alopecia is described. Loss of scalp hair is one of the most visible and most frequently occurring early side-effects of chemotherapy; generally it is considered to be completely reversible after cessation of treatment, except after busulfan. However, patients occasionally experience incomplete regrowth. We performed hair root examination in 12 patients with poor regrowth of scalp hair 12 years (range 8-16) following completion of chemotherapy. Hair roots were classified microscopically into anagen, catagen or telogen growth phase and the number of dysplastic and dystrophic hair roots was assessed. The results were compared to normal values known from literature. In all 12 patients we found a decreased percentage of anagen hair roots; 11/12 patients had an increased percentage of dysplastic and dystrophic hair roots. We concluded that permanent damage of hair roots may occur as a late effect of chemotherapy.

In the general discussion **(chapter 7)** we briefly review questions and controversies concerning the disorders, studied in this thesis. We stress the need for long-term follow-up of these patients with the following purposes: 1) patient care; 2) feed-back to current and future treatment protocols; 3) research on late effects of cancer treatment. Finally we make some suggestions for the future.