Bone mineral density, thyroid function, and gonadal status in young adult survivors of childhood cancer

Eryk Latoch[1], Katarzyna Muszyńska-Rosłan[1], Agata Panas[1], Anna Panasiuk[1], Beata Rutkowska-Żelazowska[2], Jerzy Konstantynowicz[3], Maryna Krawczuk-Rybak[1]

[1]Department of Pediatric Oncology and Hematology, Medical University of Bialystok, Bialystok, Poland
[2]Department of Pediatric Laboratory Diagnostics, Medical University of Bialystok, Bialystok, Poland
[3]Department of Pediatrics and Developmental Disorders, Medical University of Bialystok, Bialystok, Poland

Introduction: During the last years, changes in the diagnosis and treatment have caused a significant increase of the number of young adults who experienced cancer in childhood. This enlarging population is affected by many health problems, including multiple hormone deficiencies and bone mineral deficits. This is the first polish study assessing bone mineral density and endocrine status in young adult cancer survivors.

Material and methods: A total of 76 long-term survivors treated for pediatric cancer were identified. The mean age at the time of study was 24.1 ±3.5 years. Bone mineral density and TSH, fT3, fT4, FSH, LH, estradiol and testosterone level were assessed for each patient.

Results: Nine subjects were diagnosed with subclinical hypothyroidism. We found higher level of TSH in the study group, in comparison with control group (p = 0.015). Eighteen patients had increased level of FSH. In the study group higher number of patients with high FSH level was found in comparison with the control group (p = 0.049). A low BMD was observed in 7 patients whereas mild BMD deficits were found in 19 participants.

Conclusions: In conclusion, our data show that young adult cancer survivors might experienced various hormonal problems including low bone mass, thyroid impairment and gonadal dysfunction. Some of the patients required treatment, but they were not diagnosed before this study. There is the lack of proper clinical assessment among adult childhood cancer survivors in Poland. Therefore, we demonstrated the need for a comprehensive plan for longitudinal follow-up for late effects in these population.

Key words: childhood cancer, late effects, low bone mass, hypothyroidism, gonadal dysfunction, survivors.

Contemp Oncol (Pozn) 2015; 19 (2): 142–147
DOI: 10.5114/wo.2014.44123

Introduction

During the last years, changes in diagnosis and treatment have caused a significant increase in the number of young adults who experienced cancer in childhood. With the current treatments protocols the 5-year event-free survival (EFS) is over 80% [1, 2]. According to one of the world's largest studies (Childhood Cancer Survivors Study) based on 10,397 participants, there are 62.3% of survivors with at least one chronic condition and 27.5% with severe or life-threatening sequelae. It has also been estimated that 70% of pediatric cancer survivors will develop at least one medical complication or disability within 30 years from the time of diagnosis [3, 4].

This enlarging population is affected by many health problems, including multiple hormone deficiencies and bone mineral deficits. Endocrine disorders are among the most frequently reported complications in pediatric cancer survivors, affecting up to 50% of patients [5, 6]. Some, but not all, studies have shown that reduced bone mineral density (BMD) is an important consequence occurring after childhood cancer [7–12].

Despite many available data in this field, the influence of endocrinological disorders on bone mineral density is still unclear.

Nowadays, with the increasing life expectancy, it is necessary to identify patients at high risk for developing late effects of pediatric cancer and its treatment early. Furthermore, continuous follow-up of these individuals seems to be of utmost importance.

This is the first Polish study assessing bone mineral density and endocrine status in young adult cancer survivors.

Material and methods

A total of 76 long-term survivors (43 men and 33 women) treated for pediatric cancer at the Department of Pediatric Oncology and Hematology of the Medical University of Bialystok were identified. Among those 29 (38%) had leukemia, 27 (36%) lymphoma and 20 (26%) were diagnosed with solid tumors. The mean age at the time of study was 24.1 ±3.5 (range 18–34) and the average time from the end of treatment was 11.9 ±5.2 years. All patients were treated according to international protocols approved by the Polish Pediatric Leukemia/Lymphoma Study Group. All of them were in complete con-

tinuous remission. A bone marrow transplantation (BMT) procedure was performed in 6 patients treated previously for leukemia.

Written informed consent was obtained from all subjects and the study was approved by the Ethics Committee of the Medical University of Bialystok.

An overview of all medical records was performed to obtain data concerning age and type of diagnosis, and DXA results at the time of diagnosis, if available. During an interview, each participant was asked questions to determine previous fractures, current diet, medical history and use of medications. All patients underwent clinical examination and anthropometric measurement during the follow-up visit. Weight was measured on an electronic scale (Seca, Germany) and height was taken using a Martin anthropometer. Abnormal height was defined as below the third percentile for a given gender at 18 years of age according to the Polish reference data [13]. In order to classify underweight, overweight and obesity we used the BMI International Classification by WHO. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist-hip ratio (WHR) was assessed as a marker for visceral fat.

Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry (DXA) (DPX-L, GE-Healthcare Lunar, Madison, WI), which provided *Z*-scores for total body mineral density (T BMD, g/cm^2) and lumbar spine (LS BMD g/cm^2). Results of the study subjects were compared to their age- and sex-matched controls in accordance with the manufacturer's database. According to the official position of the International Society for Clinical Densitometry we used the *Z*-score instead of the World Health Organization classifications (*T*-score). Consequently, low bone density was defined as a *Z*-score ≤ –2, and osteoporosis as a *Z*-score ≤ –2 accompanied by clinically significant fracture history [14]. Due to the fact that just a few patients met the criteria of low BMD and following the other authors [15, 16] we decided to also use another cutoff point in order to show mild BMD deficits. The cutoff was set as a *Z*-score ≤ –1. The rationale for this approach is that those with lower bone mineral density are presumably to remain in the low end of the normal range [8] and reach a lower peak bone mass [17]. Additional, any bone mineral deficits might predispose young adults to an increased risk of fracture in the future [18].

Table 1. Patient characteristics, *n* (%) or mean ±SD

Parameter	Total	Leukemia	Lymphoma	Solid tumor
Patients	76	29 (38)	27 (36)	20 (26)
Sex				
male	43 (57)	18 (42)	14 (32)	11 (26)
female	33 (43)	11 (33)	13 (39)	9 (21)
Age at DXA scan (years)	24.13 ±3.48	23.72 ±2.56	25.40 ±4.11	23.01 ±3.35
Time after treatment (years)	11.88 ±5.19	12.11 ±5.12	11.48 ±4.07	12.09 ±6.69
Height [m]	1.72 ±0.09	1.72 ±0.1	1.73 ±0.07	1.74 ±0.08
Weight [kg]	70.96 ±14.91	71.75 ±15.33	71.27 ±14.85	68.14 ±13.61
Body mass index (BMI)	23.7 ±3.99	24.19 ±3.76	23.7 ±3.63	22.59 ±4.2

Table 2. Total body bone mineral density (T BMD) and lumbar spine bone mineral density (LS BMD) *Z*-scores, n (%) or mean ±SD

	Mean ±SD	Range	Number (%), patients < –1	Number (%), patients < –2
Total patients (*n* = 76)				
T BMD and/or LS BMD	–	–	19 (25)	7 (9)
T BMD	–0.084 ±0.096	–2.190–2.120	8 (10.5)	1 (1.3)
LS BMD	–0.377 ±1.192	–2.730–2.340	17 (22.4)	6 (7.9)
Leukemia patients (*n* = 29)				
T BMD	–0.103 ±1.011	–1.960–2.120	4 (13.8)	–
LS BMD	–0.692 ±1.138	–2.730–1.480	9 (31)	4 (13.8)
Lymphoma patients (*n* = 27)				
T BMD	–0.113 ±1.011	–2.190–1.930	4 (14.8)	1 (3.7)
LS BMD	–0.143 ±1.119	–2.410–1.830	4 (14.8)	1 (3.7)
Solid tumor patients (*n* = 20)				
T BMD	–0.011 ±0.613	–0.780–1.060	–	–
LS BMD	–0.128 ±1.221	–2.090–2.340	4 (20)	1 (5)

All laboratory tests were performed after an 8-hour overnight fast. Blood samples were acquired by venipuncture. An automatic system for chemiluminescence analysis (Immulite 1000, Siemens, Washington, D.C.) was used to assay serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, or testosterone levels and an Elecsys analyzer (®System, Roche, USA, Indiana) was used to measure serum thyroid-stimulating hormone (TSH), triiodothyronine (fT3) and thyroxine (fT4) levels. Current disease status information was based on patient's clinical history. Participants with high TSH and normal/low fT4 were diagnosed with subclinical or clinical hypothyroidism. Those with a high LH and/or FSH or low LH and/or FSH level were considered to have suspected gonadal dysfunction. All hormonal results were compared to the control group which consisted of 49 healthy young adults.

Statistical analysis was performed with STATA version 11.0 (StataCorp, College, Texas). Data were expressed as means ± standard deviation (SD), or median and quartiles when appropriate. In the univariate analysis, Fisher's exact test and χ^2 test were used, whereas continuous variables were compared with the Mann-Whitney test or Student *t*-test. Analysis of variance (ANOVA) was used to assess the relationship between diagnosis and bone mineral density. The Wilcoxon test was used to determine the magnitude of differences between matched groups. A p value < 0.05 was considered significant.

Results

A total of 76 white young adults, 33 men (43%) and 43 women (57%), were enrolled in the study. The mean age at the follow-up visit was 24.1 years ±3.5 (range 18–34). Depending on diagnosis, patients were divided into three groups: leukemia, lymphoma and solid tumors. The characteristics of each group are shown in Table 1. No statistically significant difference was observed between groups for sex, age at DXA scans or time after treatment.

Anthropometry

Seventy-four out of 76 patients had reached the final height at the time of the study. We found one female treated for hypothyroidism with an abnormal height (1.43 m) and one man with normal hormonal status who presented a low height (1.63 m). At the follow-up visit 15 (19.7%) patients were overweight (BMI ≥ 25), 7 (9.2%) were obese (BMI > 30), whereas 50 (65.8%) had a normal body mass index (BMI). We found 4 underweight patients (5.3%) (BMI < 18.5). The mean WHR ratio was 0.82 and 0.88 for women and men, respectively. No significant differences in height, weight, BMI and WHR were found between groups according to the diagnosis. We observed greater values of these parameters in men than in women ($p < 0.05$).

Thyroid gland

Thyroid tests (fT3, fT4 and TSH) were carried out in a total of 72 patients. During the follow-up visit 4 patients were on thyroid hormone replacement therapy. Nine subjects (12.5%) with high TSH and normal fT3 and fT4 levels (4 male and 5 female) were diagnosed with subclinical hypothyroidism (4 patients were diagnosed with ALL, 3 with Hodgkin lymphoma, 1 with Wilms tumor and 1 with soft tissue sarcoma; all of them were treated in accordance with relevant protocols approved by the Polish Pediatric Leukemia/Lymphoma Study Group at the time). Among these patients, 2 were treated with levothyroxine at the time of the study, whilst 7 did not receive any treatment. One female was on thyroid hormone substitution and was in euthyreosis. Another patient, who underwent strumectomy because of thyroid cancer, had an increased level of fT4 during treatment with levothyroxine. No other cases with any second neoplasm were found in the analyzed group. There was no significant difference in the number of patients with thyroid hormone disorders between leukemia, lymphoma or solid tumor groups. We found a higher level of TSH in the study group, in comparison with the control group (2.65 ±1.4 mIU/l vs. 1.99 ±0.97 mIU/l respectively, $p = 0.015$). These values were however within normal ranges and there was no statistical difference in the number of patients with subclinical hypothyroidism between study and control groups.

Gonads

Assessment of gonadal function (FSH, LH, estrogen, testosterone) was performed in a total of 74 patients. Two females were treated with hormone replacement therapy (HRT). In the first case abdomen radiotherapy was used because of Wilms tumor, while the second patient was treated with total body irradiation during acute lymphoblastic leukemia therapy. Eleven participants (6 female) had increased levels of both LH and FSH. Among these patients 3 females had abnormal estrogen concentration (2 out 3 were treated with HRT). An additional 7 patients (2 female) had only FSH level increased. One female with decreased gonadotropins (LH, FSH) and a normal estrogen level was reported. All male subjects had a normal testosterone level. In the study group we found a higher number of patients with a high FSH level in comparison with the control group (18/74 vs. 5/49, respectively; $p = 0.049$).

Bone mineral density

Table 2 shows total body and lumbar spine bone mineral density (expressed in *Z*-scores) and the number of patients with low mineral density as well. There were no significant differences in the mean T BMD *Z*-scores (Fig. 1) and LS BMD *Z*-scores (Fig. 2) between survivors of leukemia, lymphoma or solid tumors. A low BMD (defined as a T BMD and/or LS BMD *Z*-score ≤ –2) was observed in a total of 7 out of 76 patients (9%) whereas mild BMD deficits (defined as a T BMD and/or LS BMD *Z*-score ≤ –1) were found in 19 participants (25%) – 8 women and 11 men. Nine of them were diagnosed with leukemia, 5 with lymphoma and 4 with solid tumors. Cranial radiation therapy (18 Gy) was used in 9 cases as part of comprehensive treatment of acute lymphoblastic leukemia (ALL).

There were no statistically significant differences in hormonal abnormalities between patients with normal and abnormal bone mineral density ($p < 0.05$). We also did not find any differences in the number of subjects with

low BMD depending on whether they had endocrine disturbances or not. In the whole study group, 3 participants with both high TSH and FSH/LH levels were found (1 of them had low bone mass). Among patients who received bone marrow transplantation (6/76), bone mineral deficits were noted in 2 cases.

In the correlation analysis we did not find any significant relations between T BMD *Z*-score and TSH (r = –0.08, p = 0.51), LS BMD *Z*-score and TSH (r = –0.12, p = 0.37), T BMD *Z*-score and fT3/fT4 (r = –0.04, r = –0.30; p = 0.76, p = 0.34 respectively), LS BMD *Z*-score and fT3/fT4 (r = –0.10, r = –0.14; p = 0.43, p = 0.31 respectively), as well as between T BMD, LS BMD and LH/FSH level ($p > 0.05$). Results on bone mineral density were analyzed for the whole group, and separately for males and females.

Among all patients, we identified 34 subjects who had a DXA scan at the time of diagnosis and we compared it with the DXA results at the time of our study. We did not note any significant differences in densitometry outcomes (*Z*-scores for T BMD and LS BMD).

No patient was diagnosed with osteoporosis according to the International Society for Clinical Densitometry [14].

Fractures

In accordance with the ISCD recommendations a clinically significant fracture history is one or more of the following: long bone fracture of the lower extremities, vertebral compression fracture and two or more long-bone fractures of the upper extremities. In the study group, 27 patients had a fracture history. Only 2 of them were clinically significant and all occurred at the time of treatment. None of these patients had hormonal abnormalities.

Discussion

Endocrinological disturbances, reduced bone mineral density and high risk of fractures are considered as results of childhood cancer and treatment management [5]. The major factors increasing the risk of these late complications are mainly associated with the disease itself and its treatment (glucocorticoids, multi-agent chemotherapy and the amount as well as location of radiotherapy) [9, 19]. The aim of this study was to assess BMD and endocrine status in young adult cancer survivors. We did not analyze treatment-related factors separately. The reason for this was the fact that a long time has elapsed since the diagnosis and therefore the authors did not have full access to all medical reports. All patients were treated according to various protocols accepted by the Polish Pediatric Group for Leukemia and Lymphoma Treatment. To our knowledge, this is the first Polish study to describe hormone complications and bone status in young adult cancer survivors.

Both height and weight are closely related to endocrine status. Therefore, anthropometry cannot be ignored when discussing the hormonal disturbances.

It has been established that anticancer treatment might reduce growth in children [20]. Radiotherapy is one of the most known factors which increase the likelihood of height deficits even when the cranial dose is 12 Gy [21, 22]. Moreover, approximately 70% of patients who did not receive cranial radiation during therapy show catch-up growth several years after completion of treatment [23]. In our study 2 patients had height below the normal range [1 of them received cranial radiation as part of acute lymphoblastic leukemia (ALL) treatment]. The other participants reached normal height.

Obesity is considered one of the most important chronic diseases in the general population. Survivors of childhood cancer are particularly vulnerable to abnormal weight gain [24]. Among our patients 22 (28.95%) had BMI equal to or above 25 kg/m^2. Despite the fact that we did not find any differences between groups of adults with different previous pediatric cancer diagnosis, our study showed a high percentage of patients with abnormal BMI. This is in accordance with the latest world's largest study in this field [24, 25]. However, when we compared it to the Polish WHO POL-MONICA-BIS Study we did not notice any significant differences [26].

Patients after completion of antineoplastic therapy can develop thyroid gland abnormalities. Primary hypothyroidism, hyperthyroidism and thyroid cancer have been reported to occur at a higher rate in survivors compared with the general population [6]. Hypothyroidism is common among children who have been treated with chest or mantle radiotherapy for Hodgkin's disease, craniospinal radiation for central nervous system tumors, and total body irradiation before stem cell transplantation. One of the world's largest studies (CCSS) based on 13,674 participants with Hodgkin's lymphoma showed increased risk of hypothyroidism with an increased dose of radiation ≥ 4500 cGy (RR 10.7; 95% CI: 4.7–30.6), time since diagnosis < 5 years (RR 2.1; 95% CI: 1.7–2.6), age at diagnosis > 15 years (RR 1.5; 95% CI: 1.2–1.9) and female sex (RR 1.7; 95% CI: 1.4–2.1). Relative risk for hypothyroidism was 16.1 times higher in comparison to siblings in the control group. Higher risks for nodules and hyperthyroidism have been reported as well [21, 23]. In our study we found 9 young adults (12.5%) with subclinical hypothyroidism, whereas in the general population it reaches 10% and occurs mainly in older age [27]. Interestingly, in 7 patients hypothyroidism was first diagnosed during this study, which shows the importance for thyroid function screening in survivors.

Despite the fact that we did not notice any differences in the number of patients with thyroid abnormalities between the study and control group, a higher level of TSH in the study group was found. This finding might indicate higher risk of hypothyroidism in the future.

The negative effects of cancer treatment on reproductive functions are well known. Gonadal damage might be caused by alkylating agents which have a particularly detrimental impact on testicular/ovarian function. They include cyclophosphamide, chlorambucil, melphalan and busulfan. Similar effects are shown by other chemotherapeutic agents – cisplatin, procarbazine or cytarabine [28]. All of the listed drugs were used during anticancer treatment of patients from the study group. Gonadal dysfunction can result in premature menopause in women or infertility in both genders. It has been established that radiation therapy (directly to the gonads or to the brain) has caused gonadal damage. Younger females are more resistant to treatment-induced failure than older female

patients, because of increased numbers of follicles. However, cranial radiotherapy > 20 Gy produces gonadal failure in most children [23]. Tromp *et al.* conducted research in young adults of childhood cancer male survivors and established that one-third of participants of the study have an elevated FSH level (study based on 488 subjects). They also found that all men whose partners conceived by assisted reproductive technology had a high FSH level and all men with a normal range of FSH achieved conception naturally [29]. In our study we found a higher incidence of abnormal FSH level compared with the control group, which might indicate problems with infertility.

Several studies have shown that childhood cancer survivors are a risk group for bone mineral deficits including low bone mass and skeletal complications. The available data in this field appear to be mostly conflicting, generally due to a lack of prospective studies and insufficient data [7–9, 12, 15, 30–35]. In our research 7 (9%) patients with low bone mass and 19 (25%) patients with mild BMD deficits were identified. This finding validates the necessity of screening this population for bone mineral decrements.

Adults with gonadal dysfunction or thyroid abnormalities might present low BMD. We did not find any correlation between the hormonal disturbances and bone mineral density. The number of patients with hormonal dysfunction in our group was limited so we could not carry out a proper statistical analysis between studied groups of adults. Due to the lack of full information, fragility assessment was not performed in this study. However, we noticed the importance of fragility fractures in adult survivors' life; therefore, the risk of fractures should be determined in this group of patients.

Every patient diagnosed with hormonal abnormalities was referred to the Endocrine Outpatient Clinic.

Conclusions

Our data show that young adult cancer survivors might experience various hormonal problems including low bone mass, thyroid impairment and gonadal dysfunction. Some of the patients required treatment, yet they were not diagnosed before this study. Furthermore, it seems that subclinical development of endocrine diseases might increase the number of complications in later life. There is a lack of proper clinical assessment among adult childhood cancer survivors in Poland. Therefore, we demonstrated the need for a comprehensive plan for longitudinal follow-up for late effects in this population.

Acknowledgement

Eryk Latoch is a scholarship holder who participates in the project 'Studies, research, commercialization – a support programme of UMB doctoral students' Sub-measure 8.2.1 Human Capital Operational Programme, co-financed from the European Union under the European Social Fund.

Supported by grant No. 113-79802L from the Medical University of Bialystok.

The authors declare no conflict of interest.

References

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1975-2000. National Cancer Institute, Bethesda. http://seer.cancer.gov/csr/1975_2000/Accessed 2013.
2. Mariotto AB, Rowland JH, Yabroff KR, Scoppa S, Hachey M, Ries L, Feuer EJ. Long-term survivors of childhood cancer in the United States. Cancer Epidemiol Biomarkeres Prev 2009; 18: 1033-40.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006; 355: 1572-82.
4. Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 2004; 54: 208-36.
5. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer 2010; 17: R141-59.
6. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivors Study cohort: a review of published findings. J Clin Oncol 2009; 27: 2339-55.
7. Gunes AM, Can E, Saglam H, Ilçöl YO, Baytan B. Assessment of bone mineral density and risk factors in children completing treatment for acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2010; 32: 102-7.
8. Kaste SC, Metzger ML, Minhas A, Xiong Z, Rai SN, Ness KK, Hudson MM. Pediatric Hodgkin lymphoma survivors at negligible risk for significant bone mineral density deficits. Pediatr Blood Cancer 2009; 52: 516-21.
9. Sala A, Talsma D, Webber C, Posgate S, Atkinson S, Barr R. Bone mineral status after treatment of malignant lymphoma in childhood and adolescence. Eur J Cancer Care (Engl) 2007; 16: 373-9.
10. Brennan BM, Shalet SM. Endocrine late effects after bone marrow trans plant. Br J Haematol 2002; 1: 58-66.
11. Nysom K, Holm K, Michaelsen KF, Hertz H, Müller J, Mølgaard C. Bone mass after treatment of malignant lymphoma in childhood. Med Pediatr Oncol 2001; 37: 518-24.
12. Aisenberg J, Hsieh K, Kalaitzoglou G, Whittam E, Heller G, Schneider R, Sklar C. Bone mineral density in young adult survivors of childhood cancer. J Pediatr Hematol Oncol 1998; 3: 241-5.
13. Palczewska J, Niedźwiecka Z. Siatki centylowe do rozwoju somatycznego dzieci i młodzieży. Zakład Rozwoju Dzieci i Młodzieży. Instytut Matki i Dziecka. Warszawa 1999. http://www.wczp-lodz.pl/Dokumenty/siatki_centylowe.pdf.
14. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S. Official position of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Position Development Conference. J Clin Densitom 2008; 11: 75-91.
15. Thomas IH, Donohue JE, Ness KK, Dengel DR, Baker KS, Gurney JG. Bone mineral density in young adult survivors of acute lymphoblastic leukemia. Cancer 2008; 11: 3248-56.
16. Polgreen LE, Petryk A, Dietz AC, et al. Modifiable risk factors associated with bone deficits in childhood cancer survivors. BMC Pediatrics 2012; 12: 40.
17. Baxter-Jones AD, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. J Bone Miner Res 2011; 8: 1729-39.
18. Clark EM, Ness AR, Bishop NJ, Tobias JH. Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res 2006; 9: 1489-95.
19. Mulder JE, Bilezikian JP. Bone density in survivors of childhood cancer. J Clin Densitom 2004; 4: 432-42.
20. Viana MB, Vilela MI. Height deficits during and many years after treatment for acute lymphoblastic leukemia in children: a review. Pediatr Blood Cancer 2008; 50: 509-16.
21. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivors Study. J Clin Endocrinol Metab 2000; 85: 3227-32.
22. Paulino AC, Jhaveri P, Dreyer Z, Teh BS, Okcu MF. Height impairment after lower dose cranial irradiation in children with acute lymhoblastic leukemia. Pediatr Blood Cancer 2011; 56: 279-81.
23. Dickerman JD. The late effects of childhood cancer therapy. Pediatrics 2007; 119: 554-68.

24. Green DM, Cox CL, Zhu L, et al. Risk factors for obesity in adult survivors of childhood cancer: a report from The Childhood Cancer Survivors Study. J Clin Oncol 2012; 30: 246-55.
25. Meacham LR, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL, Oeffinger KC. Body mass index in long-term adult survivors of childhood cancer. A report of the Childhood Cancer Survivors Study. Cancer 2005; 8: 1730-9.
26. Kopeć G, Podolec P. Rozpowszechnienie nadwagi i otyłości w Polsce i na świecie. Polskie Forum Profilaktyki Chorób Układu Krążenia 2007; 8: 3.
27. Krysiak R, Marek B, Okopień B. Subkliniczna niedoczynność tarczycy. Wiadomości Lekarskie 2008; 4-6: 139-45.
28. Krawczuk-Rybak M. Powikłania narządowe leczenia skojarzonego wczesne i odległe. Chybicka A, Sawicz-Birkowska K. Onkologia i hematologia dziecięca. Wydawnictwo Lekarskie PZWL, Warszawa 2008; 1054-6.
29. Tromp K, Claessens JJ, Knijnenburg SL, van der Pal HJ, van Leeuwen FE,Caron HN, Beerendonk CC, Kremer LC. Reproductive status in adult male long-term survivors of childhood cancer. Hum Reprod 2011; 7: 1775-83.
30. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiashvili N, Mattano LA, Meacham LR. Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. Pediatrics 2008; 3: 705-13.
31. van Beek RD, van den Heuvel-Eibrink MM, Hakvoort-Cammel FG, et al. Bone mineral density, growth, and thyroid function in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy only. J Clin Endocrinol Metab 2009; 6: 1904-9.
32. Le Meignen M, Auquier P, Barlogis V, et al. Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoetic stem cell transplantation and other treatment modalities. Blood 2011; 6: 1481-9.
33. Muszynska-Roslan K, Panasiuk A, Latoch E, Krawczuk-Rybak M, Konstantynowicz J. Little evidence of low bone mass in acute lymphoblastic leukemia survivors. J Clin Densitom 2011; 1: 108-15.
34. Müller C, Winter CC, Rosenbaum D, Boos J, Gosheger G, Hardes J, Vieth V. Early decrements in bone density after completion of neoadjuvant chemotherapy in pediatric bone sarcoma patients. BMC Musculoskelet Disord 2010; 11: 287.
35. Benmiloud S, Steffens M, Beauloye V, de Wandeleer A, Devogelaer JP, Brichard B, Vermylen C, Maiter D. Long-term effects on bone mineral density of different therapeutic schemes for acute lymphoblastic leukemia or non-Hodgkin lymphoma during childhood. Horm Res Paediatr 2010; 74: 241-50.

Address for correspondence

Eryk Latoch, MD
Department of Pediatric Oncology and Hematology
'Dr Ludwik Zamenhof' Children's Teaching Hospital
Medical University of Bialystok, Poland
Waszyngtona 17, 15-274 Białystok
tel./fax +48 85 745 08 46
e-mail: eryklatoch@gmail.com

Submitted: 14.10.2013
Accepted: 4.06.2014