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High prevalence of late adverse events in malignant bone tumour survivors diagnosed at adult age

A.C.M. van de Luijtgaarden[1]*, L. Kapusta[2,6], L. Bellersen[3], J.P.M. Bokkerink[4], S.E.J. Kaal[1], Y.M.H. Versleijen-Jonkers[1], H.W.B. Schreuder[5], W.T.A. van der Graaf[1]

Departments of [1]Medical Oncology, [2]Children's Heart Centre, [3]Cardiology, [4]Paediatrics, [5]Orthopaedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands, [6]Department of Pediatric Cardiology ,Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel, *corresponding author: tel.: +31(0)24-3610345, fax: +31(0)24-3540788, email: Addy.vandeLuijtgaarden@radboudumc.nl

ABSTRACT

Background: Late treatment-related adverse events are particularly prevalent in survivors of childhood bone cancer because of the combination of cytotoxic drugs, major surgery and radiotherapy. Existing studies for late toxicity in survivors of Ewing's sarcoma (ES) and osteosarcoma (OS) diagnosed at adult age have focused on specific sequelae. We investigated a broad spectrum of potential late effects in these patients.

Methods: Relapse-free OS and ES patients aged ≥ 16 at diagnosis and treated at the Radboud University Medical Centre (1982-2007) were invited for systematic late toxicity screening. This included history taking, physical examination, echocardiogram, bone densitometry, audiogram, and serum and urine screening for renal toxicity and infertility. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 3.0.

Results: In 24 survivors (63% male, mean age at screening 45.7 years, mean follow-up 10.9 years, 70% OS) we found a median of eight adverse events. Frequent findings included abnormal gait, osteoporosis, pain, left ventricular systolic dysfunction, obesity and nephropathy. The maximum grade of any adverse event was mild in four (17%), moderate in 11 (46%), severe in six (25%), and disabling in three cases (13%). There was a trend towards more events in patients diagnosed at an older age.

Conclusion: The incidence of late adverse events in this study of survivors of bone tumours diagnosed at adult age is higher than in any previously published childhood cancer survivorship study. Older patients seem to be particularly at risk. Our findings underscore the need for systematic screening of late effects in bone cancer survivors of adult age at diagnosis.

KEYWORDS

Bone neoplasms, drug therapy, osteosarcoma, sarcoma, Ewing's, survivors

INTRODUCTION

Bone sarcomas are rare tumours with an annual incidence of 1/100,000. Osteosarcoma (OS) and Ewing's sarcoma (ES) are well-known subtypes requiring intensive therapy. OS has a bimodal age distribution with its first peak incidence in the second and third decade of life and a smaller peak in the seventh decade; ES mainly occurs in the second decade.[1] Before the use of chemotherapy, survival was limited to only about 20% because of an almost universal development of metastases. The current treatment strategy consists of multi-agent chemotherapy and surgery. Radiotherapy may also be applied in ES. This approach yields a dramatically improved cure rate of 50-70% in patients with localised disease. Patients with metastatic disease have a poorer prognosis, but cure is still possible.[2] With such cure rates the risk of development of late therapy-related adverse events becomes relevant. While most childhood cancer survivor studies have focused on a single late adverse event, three retrospective cohort studies evaluating 14,372 (Childhood Cancer Survivor Study, CCSS),[3] 1284 (Polikliniek Late Effecten Kindertumoren, PLEK)[4] and 519 (Children's Healthcare of Atlanta, CHOA)[5] survivors of any childhood malignancy have evaluated the overall health status of study participants. In all studies, the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, CTCAE was used to grade cancer treatment-related adverse event severity as 1 (mild), 2 (moderate), 3 (severe), 4 (disabling or life-threatening) or 5 (event-related

death).[6] All three studies conclude that late treatment-related complications are highly prevalent amongst childhood cancer survivors (*table 1*). CCSS and PLEK further show that survivors of bone tumours are especially at risk; CHOA reports similar findings for sarcoma in general. Based on these papers, lifelong medical surveillance of childhood cancer survivors is now common practice for paediatricians. Because of the specific age distribution, an important number of bone sarcoma patients are, however, cared for by medical oncologists for whom long-term follow-up for treatment sequelae of patients with bone cancer is not part of the routine. It is as yet unknown whether survivors of bone cancer diagnosed in adolescence or adulthood suffer from a comparable percentage and kind of adverse events. In this regard, though all subjects were under 20 years of age, those who were older at the time of diagnosis in the CCSS study were more likely to report any condition, conditions of grades 3-5, or multiple conditions ($p < 0.001$). In the CHOA cohort, older patients (≥ 10 years at diagnosis) were also at risk for conditions of grades 3-5 ($p < 0.01$).

We initiated the present study, aiming to characterise the point prevalence and severity of late adverse events in a cohort of relapse-free survivors of OS or ES diagnosed in adulthood. In addition, we sought to identify subpopulations at the highest risk for chronic health conditions.

PATIENTS AND METHODS

We identified all patients who had been treated for OS or ES at the Radboud University Medical Centre between 1982-2007. Patients needed to have been at least 16 years or older at diagnosis, treated at the Department of Orthopaedic Surgery, Medical Oncology (EORTC 80861: four patients; EORTC 80931: one patient; CESS86: one patient; EuroEwing99: two patients, Off-protocol cisplatin/doxorubicin: nine patients; the remainder of patients treated off-protocol individually) and/or radiotherapy, and currently alive and relapse free in order to be eligible for systematic screening for late toxicity. Details about cancer diagnosis and therapy were extracted from the patient file. The current health status and address were checked with the patient's general practitioner if more than one year had elapsed since the last visit to our hospital. The study was approved by the institutional review board and written informed consent was obtained from all participants. Screening was performed at the Medical Oncology outpatient department and consisted of physical examination and history taking, including questions on psychosocial events hampering daily life (employment, mortgage loan, life and health insurances) by a dedicated physician (AvdL), cardiac evaluation using left ventricle ejection fraction measurement with echocardiography; bone density assessment by dual energy X-ray absorptiometry (DXA; whenever applicable, femur neck bone density was measured on the unaffected side) and a pure tone audiogram to evaluate ototoxicity. Serum and urine screening were performed for renal toxicity (glomerular filtration rate, fractional calcium, magnesium and potassium excretion, urinary α1-microglobulin excretion and tubular threshold for phosphate (TmP/GFR)), fertility state (sex hormone levels and inhibin B) and metabolic syndrome trait (lipid profile, fasting glucose).

Adverse events including cardiotoxicity were graded according to the CTCAE version 3.0 unless otherwise specified.[6] Metabolic syndrome trait was defined according to the International Diabetes Federation consensus worldwide definition and graded in the Syndrome – other category as moderate,[7] Tubulopathy was defined as presence of decreased tubular phosphate reabsorption TmP/GFR < 0.80 mmol/l and increased urinary a1microglobulin excretion > 13 mg/g creatinine and graded in the Metabolic/Laboratory – Other category as mild when serum electrolyte levels were normal, moderate if electrolyte suppletion was necessary and severe if hospitalisation was needed. Male infertility was graded as mild when no sperm count was available but the serum follicle-stimulating hormone was > 10 U/l and inhibin B below the lower limit of normal,[8] otherwise the CTCAE grading was used. The prevalence of late events was calculated and treatment-related risk factors were interrogated with logistic regression analysis. Odds ratios were converted into relative risks according to the method of Zhang and Yu.[9] All analyses were performed using SPSS version 16.0 and a $p < 0.05$ was considered significant.

Table 1. *Summary of number and severity of adverse events in screening studies*

	PLEK	CCSS	CHOA	Current study
Number of adverse events per subject				
None	19.8%	37.4%	12.1%	0%
1	74.5%	62.3%	87.9%	0%
> 1	59%	37.6%	70.9%	0%
≥ 3	44.7%	23.8%	50.3%	100%
Maximum severity of adverse event				
Grade ≥ 3	36.8%	27.5%	36.4%	38%

CCSS = Childhood Cancer Survivor Study[3]; PLEK = Polikliniek Late Effecten Kindertumoren[4]; CHOA = Children's Healthcare of Atlanta[5].

RESULTS

Based on review of the patient files, 32 survivors met our eligibility criteria. Of note, of the patients who did not survive, two died because of severe cardiomyopathy.

Of the survivors five patients could not be contacted. Three patients refused to participate. Therefore, 24 of 27 contacted patients were included in our study. Characteristics of the participants are presented in *table 2*. Patients were aged 34.4 years at diagnosis (mean, range 16-63 years).

Adverse events

We scored the point prevalence of adverse events at the time of the screening visit. There were no patients without adverse events (*table 1*). The median number of events per patient was eight (range 3-12, mean 7.8). A wide range of adverse events was seen (*figure 1*). The most frequently observed events (≥ 50% of the cohort) included musculoskeletal-related symptoms, i.e. abnormal gait, abnormal joint function and pain. Osteoporosis, obesity and tubular nephropathy also affected ≥ 50% of patients. In 29% of patients, potentially treatable occult cardiomyopathy was found. The maximum severity of reported adverse events was as follows: mild in four patients (17%), moderate in 11 (46%), severe in six (25%) and disabling in three (13%). Severe or disabling late therapy-related effects (i.e. 3 grade 3) included impaired joint function, abnormal gait, obesity and low serum phosphate.

Table 2. *Demographic and treatment data*

Patient characteristics		
N		24
Sex	Male	15 (63%)
	Female	9 (38%)
Diagnosis	Osteosarcoma	17 (70%)
	Ewing's sarcoma	7 (30%)
Age at diagnosis *mean (range)*		34.4 years (16-63)
Follow-up *Mean, median (range)*		10.9 years, 6.2 years (2-27)
Age at screening *mean (range)*		45.7 years (19-66)
Treatment	Surgery only	13%
	Chemotherapy and surgery	75%
	Chemotherapy and radiotherapy	4%
	Chemotherapy, surgery and radiotherapy	8%
Chemotherapy	Anthracyclines ± other chemotherapy	46%
	Anthracyclines and alkylating agents ± other chemotherapy	42%
Cumulative anthracycline dose *median (range)*		330 mg/m² (0-518, SD 164)

Psychosocial events

Several patients reported psychosocial problems that could be attributed to cancer survival; three had difficulties obtaining a mortgage loan, three reported problems with life insurance, two had increased health insurance contributions and four were unwillingly unemployed. Because grading criteria for these events are lacking in the CTCAE criteria, these events are not included in the following analyses.

Risk factors for adverse events

Overall burden of events

Patients who were older at the time of diagnosis (OR 1.258 (95% confidence interval 1.045-1.515) RR 1.04, p = 0.016) or at follow-up (OR 1.187 (1.045-1.349), RR 1.052, p = 0.008 (with age as a continuous variable) were more likely to report more than eight adverse events. In an adjusted model combining both age parameters, age at follow-up was no longer associated with the number of reported adverse events (p = 0.952) while age at diagnosis retained a trend to significance (p = 0.083). Age was not related to the reported severity of any adverse event. Neither follow-up duration nor sex were associated with the reported number of adverse events or the maximum reported severity of any event (*table 3*).

Specific adverse events and known risk factors

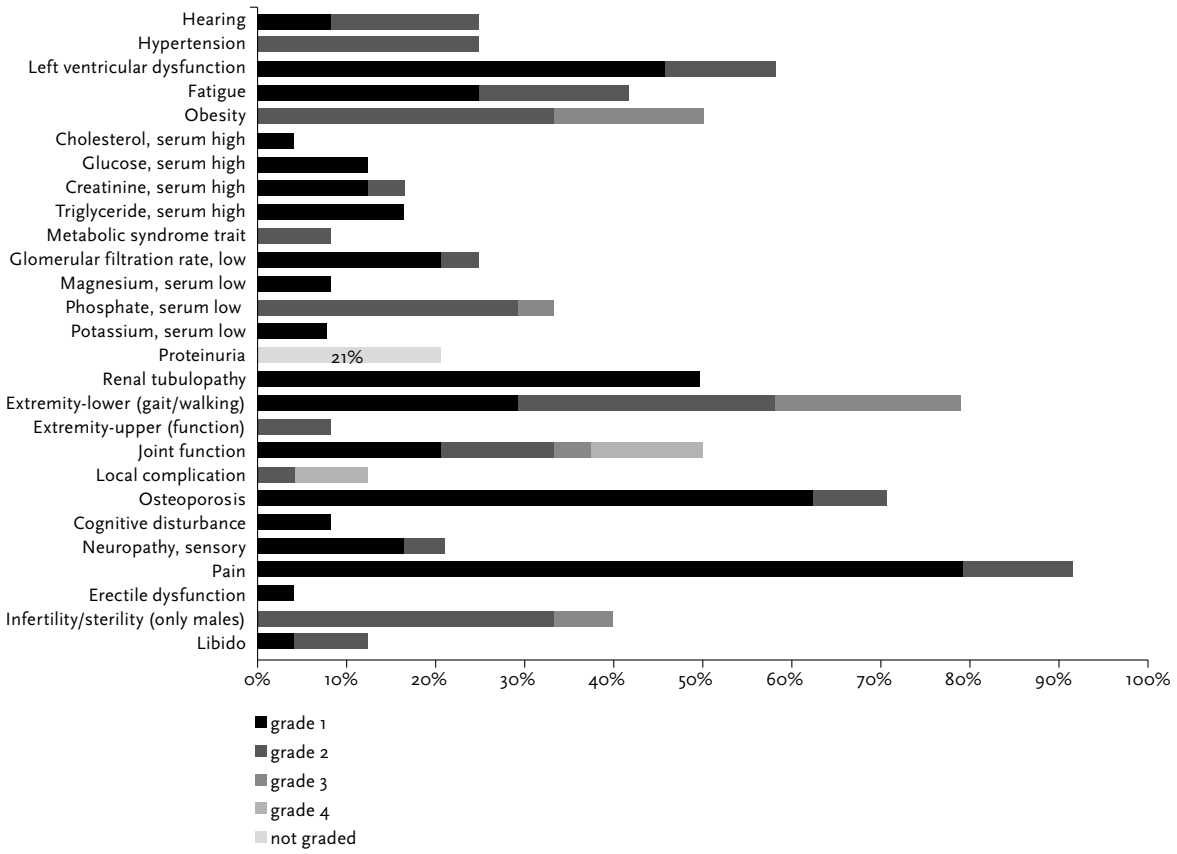
Cardiomyopathy, defined as a decreased left ventricle ejection fraction assessed by echocardiography, was more common in patients who had received a minimal dose of 350 mg/m² of doxorubicin (OR 6 (1.018-35.37), RR 2.25, p = 0.037).

We were unable to confirm other previously reported associations between specific adverse events and exposure to certain drugs, e.g. neurotoxicity and cisplatin, ifosfamide or vincristine and nephrotoxicity and cisplatin, ifosfamide or methotrexate (*table 4*).

DISCUSSION

The need for lifetime follow-up of childhood cancer survivors to timely detect and treat late adverse events is now widely recognised. Childhood cancer survivor studies show that bone cancer patients are particularly at risk for adverse events. Although bone tumours also affect adults, follow-up studies in those survivors are scarce and the available studies have focused on specific sequelae only. While our study is hampered by its retrospective inclusion and small sample size, it is the first one to assess the whole

Figure 1. *Prevalence and grade of adverse events*



Events defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, CTCAE;[6] Metabolic syndrome trait was defined according to the International Diabetes Federation consensus worldwide definition.[7] Tubulopathy was defined as presence of decreased tubular phosphate reabsorption TmP/GFR and increased urinary α1-microglobulin excretion.

spectrum of late adverse events in a systematic manner and with a standardised grading system in this age group. We add to the paucity of information by demonstrating that in a cohort of survivors of OS or ES diagnosed in adulthood, the point prevalence and severity of a wide variety of late adverse events is high. In fact, there were no patients without adverse events and the number of adverse events per patient was higher than in any of the previously published large childhood cancer survivorship studies (*table 1*). Of note, since 24 of 32 eligible subjects participated (two had died from cardiotoxicity, five could not be contacted and three refused to participate), toxicity in our cohort may be subject to participation bias.

In agreement with two of these childhood survivorship studies, CCSS and CHOA,[3,5] we also observed a trend that older patients are more likely to experience a multitude of late treatment sequelae. Because all but one patient had undergone surgery such as prosthetic joint replacement, arthrodesis or even limb amputation, musculoskeletal symptoms in survivors were to be expected.[10] Indeed, the most frequently observed events in our cohort included abnormal gait (79%), abnormal joint function (50%) and pain (63%). Another striking finding of our study was the exceptionally high percentage of osteopenia (63%) with a moderate prevalence of osteoporosis (8%). In survivors of osteosarcoma, osteoporosis has previously been reported in 20.8-47.5% and osteopenia in 30-43.7%;[11,12] it is notable that studies reporting high prevalence measured bone density in affected-limb femur necks. Also in heterogeneous groups of bone sarcoma and bone and soft tissue sarcoma patients the median bone density is below normal.[13,14] Various underlying mechanisms could clarify this finding: in younger patients, renal loss of minerals, nutritional deficits, physical inactivity and irregular menstrual cycles during therapy may prevent reaching a normal peak bone mass.[12] Increased loss of bone mass may be due to immobilisation or premature ovarian failure.[11,15] However, we failed to demonstrate a correlation between osteoporosis and reported difficulty in walking as a surrogate marker for immobility. No data regarding menstrual cycles, food intake or renal mineral excretion during therapy were available and the prevalence of premature ovarian failure

is undetermined in our cohort. Hence, our findings remain partially unexplained and deserve further research.

We detected renal tubulopathy, defined as a decreased tubular phosphate threshold (TmP/GFR) and increased urinary a1-microglobulin excretion in 50% of our patients. A decreased GFR was found in 25%. Other frequently found renal toxicity markers included low serum phosphate (33%) and proteinuria (21%). These findings are in line with previously reported data.[16,17] Three key chemotherapeutic agents in bone sarcoma, cisplatin, ifosfamide and methotrexate, have all been linked to renal toxicity.[16-18] Cisplatin probably potentiates ifosfamide-induced damage[19] and in itself may cause a reduction in the GFR and hypomagnesaemia.[18,20] Methotrexate has mainly tubulotoxic effects.[21] Sample size probably prevented us from confirming the aforementioned risk factors known in the literature.

Cardiotoxicity is a well-known, often dose-related adverse side effect of anthracyclines.[23] The pathogenic mechanism is not fully understood but may include anthracycline-mediated production of free oxygen radicals, cardiomyocyte apoptosis, inhibited expression of cardiomyocyte-specific genes, calcium overload caused by activation of the calcium release channel, a direct toxic effect on the adrenergic function of the myocardium and altered molecular signalling.[24,25] Cardiomyopathy, regardless of its cause, is treated with afterload reduction by angiotensin-converting enzyme (ACE) inhibition or β-blockers.[26] In breast cancer patients, ACE inhibition established a potent and long-lasting recovery and a combination of ACEi and beta-blockers achieved normalisation of left ventricle function.[27,28] It is therefore important to detect cardiomyopathy in a timely manner. Reported frequencies of subclinical cardiotoxicity after sarcoma treatment vary between 27-100% and overt heart failure is reported in 1.5-2.2% of patients.[23,29-33] Female and older patients are particularly at risk.[25,27,33,34] It has been suggested that cisplatin is also cardiotoxic and exposure to cisplatin has mainly been associated with the development of an unfavourable cardiovascular risk profile.[35-37] In our cohort, occult cardiomyopathy was found in 29% of patients while no patients suffered from overt heart failure, but it should be noted that two patients died from late diagnosed cardiomyopathy

Table 3. *Risk factors for the overall burden of adverse events*

	Number of events ≥ 8	CTCAE ≥ 2	CTCAE ≥ 3
Age at follow-up	OR 1.187 (1.045-1.349) RR 1.052 p = 0.008	p = 0.194	p = 0.538
Age at diagnosis	OR 1.258 (1.045-1.515) RR 1.04 p = 0.016	p = 0.56	p = 0.712
Follow-up duration	p = 0.146	p = 0.144	p = 0.721
Sex (female vs. male)	p = 0.831	p = 0.999	p = 0.165

OR = odds ratio (95% confidence interval); RR = relative risk; CTCAE = Common Toxicity Criteria for Adverse Events version 3.0.

Table 4. *Possible risk factors for specific adverse events*

	DOX	DOX ≥350 mg	Sex	CDDP	IFO	MTX	VCR	ALK/ DOX	Walking
Cardiomyopathy	p = 0.058	p = 0.037 OR 6 (1.018-35.37) RR 2.25	p = 0.916	p = 0.064					
Metabolic syndrome				p = 0.873					
Proteinuria				p = 0.556	p = 0.878	p = 0.112			
Tubulopathy				p = 0.921	p = 0.529	p = 0.165			
GFR				P = 0.213	p = 0.998	p = 0.998			
Magnesium				p = 0.873					
Hearing				p = 0.157					
Neuropathy				p = 0.966	p = 0.998		p = 0.997		
Male infertility								p = 0.132	
Osteoporosis									p = 0.829

Rows = late adverse event; columns = possible risk factor; cells = p value of logistic-regression analysis; OR = odds ratio (95% confidence interval); RR = relative risk; empty cells = not tested; DOX = doxorubicin; CDDP = cisplatin; IFO = ifosfamide; MTX = methotrexate, VCR = vincristine; ALK/DOX = combination of alkylating agents (i.e. cyclophosphamide and/or ifosfamide) and doxorubicin.

before the present study. We confirmed the well-known dose-dependency of anthracycline toxicity but could not confirm the significance of age and sex as risk factors for anthracycline-induced cardiotoxicity known from the existing literature. Furthermore, although obesity and hypertension were overrepresented in our cohort compared with the normal Dutch population, metabolic syndrome trait was not more prevalent in cisplatin-treated survivors, again probably due to our limited sample size.

Ototoxicity, which we found in 25% of patients, has been linked to platinum compounds, cisplatin in particular.[38,39] Peripheral neurotoxicity may be caused by ifosfamide, cisplatin (both peripheral neuropathy) and vincristine (polyneuropathy).[40,41] Of all men in our cohort, 23% were subfertile as assessed by serum tests. There is a large body of evidence that both pre- and post-pubertal testes are susceptible to cytotoxic treatment by alkylating agents.[8] Sequential alkylating agent and anthracycline-based treatment regimens carry a significant risk of infertility.[36] The combination of alkylating agents and anthracyclines did not significantly influence the risk of infertility. Because many female patients who were not postmenopausal at diagnosis were using oral contraceptives at the time of the screening visit, a reliable estimation of the incidence of female infertility in our cohort is not possible.

Though socioeconomic consequences of ES[42] and OS[43] survivorship were not qualitatively assessed in our cohort, in contrast to recent studies in long-term OS and ES childhood cancer survivors, these adverse events were also present in many of our survivors. The psychosocial consequences need to be addressed in more detail in future studies.

In conclusion, the prevalence and severity of late adverse events in survivors of bone tumours diagnosed at adult age is strikingly high and the spectrum of events remarkably broad. There is a trend towards more adverse events with increasing age at diagnosis. The most prominent adverse events included occult cardiomyopathy, osteoporosis and nephropathy, for which interventions are available and indicated, and adverse events directly related to prior orthopaedic interventions. Our findings thus underscore the need for international guidelines for the follow-up of bone cancer survivors diagnosed at adulthood, analogous to paediatric follow-up studies and recent adolescent and young adult general follow-up guidelines.[44]

DISCLOSURES

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