Technical University of Denmark

Renal impairment and late toxicity in germ-cell cancer survivors

Lauritsen, J.; Mortensen, M. S.; Kier, M. G. G.; Christensen, I. J.; Agerbaek, M.; Gupta, Ramneek; Daugaard, G.

Link back to DTU Orbit

DTU Library
Technical Information Center of Denmark

Renal impairment and late toxicity in germ-cell cancer survivors

J. Lauritsen[1]*, M. S. Mortensen[1], M. G. G. Kier[1], I. J. Christensen[2], M. Agerbaek[3], R. Gupta[4] & G. Daugaard[1]

[1]*Department of Oncology 5073, Copenhagen University Hospital, Rigshospitalet, Copenhagen;* [2]*Finsen Laboratory, Rigshospitalet and Biotech Research and Innovation Centre (BRIC), University of Copenhagen, Copenhagen Biocenter, Copenhagen;* [3]*Department of Oncology, Aarhus University Hospital, Aarhus;* [4]*Department of Systems Biology, Center for Biological Sequence Analysis, Technical University of Denmark, Kongens Lyngby, Denmark*

Background: Treatment with bleomycin–etoposide–cisplatin (BEP) impairs renal function and increases the risk of late cardiovascular disease (CVD) and death. We investigated the influence of BEP on glomerular filtration rate (GFR) and assessed the importance of GFR changes on CVD and death in a large cohort of germ-cell cancer survivors.
Patients and methods: BEP-treated patients ($N = 1206$) were identified in the Danish DaTeCa database, and merged with national registers to identify late toxicity. GFR were measured (51Cr-EDTA clearance) before and after treatment and at 1, 3 and 5-year follow-up. The influence of BEP on GFR was evaluated with a linear mixed model. Risk factors for late toxicity were identified by a landmark analysis adjusting for covariates. The cohort was compared with the background population with standardized hospitalization/mortality rates.
Results: GFR changed (ΔGFR) −11.3%, −15.4% and −25.9% after three, four and five+ cycles of BEP. For patients with impaired renal function before treatment the changes were 4.3%, 0.0% and −12.8%, respectively. During follow-up a significant rebound of GFR was documented. Compared with the background population, all patients, irrespective of renal function, had an increased risk of CVD and death. This risk depended on chronic kidney disease stage before treatment but not after treatment. ΔGFR had no influence on risk of late toxicity [death: hazard ratio (HR) 1.06, $P = 0.50$; CVD: HR 0.97, $P = 0.61$].
Conclusions: Renal function after BEP is closely related to number of cycles, but the changes in GFR are partly reversible and have no impact on risk of CVD or death.
Key words: germ-cell cancer, nephrotoxicity, late effects, CVD, BEP

introduction

The majority of patients with germ-cell cancer (GCC) survive their disease. Accordingly the prime focus has shifted from increasing survival to improvement of survivorship. Cisplatin is part of the standard treatment of GCC [bleomycin, etoposide and cisplatin (BEP)] and renal impairment is one of the main toxicities associated with cisplatin-based chemotherapy. The toxicity is associated with the number of treatment cycles and the accumulated doses of cisplatin [1]. Previous studies on renal toxicity are based on patients treated with high doses, older treatment regimens [2, 3], or based on estimates of renal function (eGFR) and small cohorts with an inherent risk of inexactness [4, 5].

Studies on the general population show a clear correlation between renal function, as defined by the National Kidney Foundation Stages of Chronic Kidney Disease (CKD), and later risk of developing cardiovascular disease (CVD) or death [6]. Treatment with BEP enhances the risk of CVD as a late effect [7], but an association between renal function loss after chemotherapy and later CVD has not been established.

In this study, we investigate the influence of BEP on long-term renal function using measured glomerular filtration rate (GFR), and investigate whether there is an association between renal impairment, late toxicities like CVD and death in GCC patients.

materials and methods

population and treatment characteristics

Subjects eligible for inclusion ($N = 1206$) were identified in the retrospective DaTeCa database covering Danish GCC patients diagnosed 1984–2007 (for full description, see supplementary Appendix, available at *Annals of Oncology* online). Inclusion criteria were: patients with disseminated GCC (gonadal, extragonadal or relapse after stage I disease) treated with BEP

Correspondence to: Dr Jakob Lauritsen, Department of Oncology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen OE, Denmark. Tel: +45-35-45-96-82; Fax: +45-35-45-39-90; E-mail: jakob.lauritsen@regionh.dk

(three cycles or more) in standard doses [bleomycin 15 000 IU/m^2/day i.v. day 1, 8, 15, etoposide (VP-16) 100 mg/m^2/day day1–5 and cisplatin (CDDP) 20 mg/m^2/day day 1–5 every 3 weeks] or double-dose cisplatin. Initially four cycles was standard treatment. However, since 2001, three cycles has been offered in the good prognostic group. All patients included had measurements of GFR before chemotherapy.

Exclusion criteria: Other primary treatment than BEP, treatment failure or death due to GCC, total $N = 275$.

To analyze the influence of cumulative cisplatin dose, the patients were divided by number of cycles received: three cycles (300 mg/m^2 cisplatin), four cycles (400 mg/m^2) and five cycles or more or double-dose cisplatin (500 mg/m^2 or more). Hydration remained uniform over time with 2-l isotonic saline before cisplatin and additional 1–2 l after. Diuretics were only administered in special cases, and no magnesium was added to hydration. There was no predefined cutoff of renal function, where patients would not receive cisplatin-based triplets. Patients with residual tumor after chemotherapy had secondary surgery. In later years, patients with seminoma were followed with positron emission tomography (PET) and computed tomography scans and only PET-positive tumors were resected.

outcome measures

Renal function, weight, height and clinical examinations were assessed before chemotherapy, after chemotherapy and during follow-up at 1, 3 and 5 years after completion of treatment. Measurements before chemotherapy were done 1–5 days ahead of treatment, and after chemotherapy the measurements were carried out less than a week after treatment cessation. During follow-up, all assessments were made in conjunction with outpatient visits. The number of patients with a complete dataset of GFR-measurements was 275. Missing renal measurements were caused by local guidelines not stating that the measurements should be done ($N = 877$), or censuring of patients before 5 years follow-up ($N = 53$).

GFR was measured by the one sample ^{51}Cr-ethylenediaminetetra acetic acid clearance technique using two (for duplicate determination) plasma samples 200 min after tracer injection [8], and normalized to a body surface area of 1.73 m^2. CKD was defined according to National Kidney Foundation guidelines into stage I (GFR above 90 ml/min/1.73 m^2), stage II (GFR 60–89 ml/min/1.73 m^2), stage III (GFR 30–59 ml/min/1.73 m^2), stage IV (GFR 15–29 ml/min/1.73 m^2) and stage V (GFR below 15 ml/min/1.73 m^2) [9].

assessment of late toxicity

In Denmark, all citizens are assigned with a unique personal identification number. This number is recorded in the Danish Civil Registration System (CRS) [10]. By linkage to the CRS, we gained information on emigration and immigration, disappearance and death.

Data on CVD and late renal disease was obtained from the National Patient Registry, which houses data on hospital discharge from 1977– and outpatient visits since 1995, including date and diagnosis [11]. Diagnoses were coded according to 'International Classification of Diseases, 8th revision' (ICD-8) until 1991; thereafter the '10th revision' (ICD-10) was used. Information about cause of death was obtained through linkage to the Danish Register of Causes of Death [12].

Major cardiovascular events were defined at first appearance of coronary heart disease, cerebrovascular accident or heart failure in any register, either as a cause of admission or cause of death. Patients with a disease event before orchiectomy were censored. In order to compare the present cohort with the Danish background population we gathered data from Statbank.dk (Statistics Denmark), which houses information on all diagnoses from 1991– and deaths from 1984– in Denmark. Full information on definitions of disease is available in (supplementary Table S1, available at *Annals of Oncology* online).

statistics

Descriptive statistics are presented by medians and quartiles for quantitative data. GFR were analyzed on the log scale using mixed modeling with repeated measures. The explanatory variables considered were: time after initial treatment, BEP treatment, age, CKD before treatment and surgery. Results are presented back transformed with 95% confidence intervals (CIs).

The influence of renal function on late effects was analyzed with a landmark analysis on time points pre and post-chemotherapy to evaluate the importance of renal function changes caused by BEP. Cox proportional hazard model was used, and the hazard assumption was graphically assessed using log–log plots. The following covariates were included: age at treatment, smoking habits (dichotomized as ever versus never), treatment period, post-chemotherapy surgery and number of treatment cycles. As smoking habits had missing values (Table 1), a multiple imputation method (20 imputations) based on covariates, outcome and date of treatment was used [13]. Inclusion of BMI as covariate was omitted due to a high number of missing values. The missing values were regarded as missing at random. GFR was evaluated as a continuous covariate and stratified according to CKD stages. Tests for interactions were carried out where applicable.

Standardized hospitalization rates (SHRs) and standardized mortality rates (SMRs) were calculated as observed number divided by expected number of cases based on the hospitalization/mortality rate in Denmark.

Patients were censored at time of metachronous GCC ($N = 9$), emigration ($N = 28$), death ($N = 69$), disappearance from Danish Civil Registry ($N = 1$) or 30 November 2012, whichever occurred first.

A z-test of proportions was used to test for significant differences over time in demographics and treatment characteristics. P values <5% were considered significant. Statistical calculations were done using SAS (v9.3, SAS Institute, Cary, NC) and SPSS 20.0 (SPSS, Chicago, IL).

results

patient characteristics

Characteristics are listed in Table 1. A total of 1206 patients were eligible for analysis. The median age and follow-up of the total population was 31.6 [interquartile range (IQR): 25.9–39.1] and 15.2 (IQR: 9.3–21.5) years, respectively. Characteristics were consistent over time concerning disease primary, age distribution, post-chemotherapy surgery, prognostic group and CKD stage before treatment, but significant changes were noted in the remaining characteristics. In total, 387 (32.1%) patients underwent surgery for residual tumor, 2 (0.6%) of these had nephrectomy during surgery. Patients who were excluded due to death of GCC or treatment failure after BEP did not differ significantly in changes of renal function, but were significantly older than patients included in analysis (supplementary Table S2, available at *Annals of Oncology* online).

renal function

Numbers of patients with GFR measurements were 1206, 1112, 557, 353 and 322 pretreatment, post-treatment and 1, 3 and 5 years after treatment, respectively. Overall median GFR before treatment was 109 ml/min/1.73 m^2 (IQR: 99–121). Out of these, 126 patients belonged (10.5%) to CKD stage II, and 16 patients (1.3%) was in stage III. After treatment median GFR was 94 ml/min/1.73 m^2 (IQR: 83–105), 406 (36.5%) in CKD stage II and 42 (3.8%) in stage III.

Based on the mixed model, several covariates had significant influence on the changes of GFR (ΔGFR): number of treatment

Table 1. Patient characteristics at time of treatment

Year of BEP treatment	1984–1989		1990–1999		2000–2007		Total	
No. of patients included	271		521		414		1206	
Primary (%)								
St I (relapse)	79	(29.2)	163	(31.3)	145	(35.0)	385	(34.1)
Disseminated, gonadal	173	(63.8)	325	(62.4)	235	(56.8)	681	(60.3)
Extragonadal retroperitoneal	16	(5.9)	26	(5.0)	29	(7.0)	54	(4.8)
Extragonadal mediastinal	3	(1.1)	7	(1.3)	5	(1.2)	10	(0.9)
Age at treatment, years (%)								
15–24	67	(24.7)	114	(21.9)	77	(18.6)	258	(21.4)
25–34	116	(42.8)	223	(42.8)	156	(37.7)	495	(41.0)
35–44	60	(22.1)	115	(22.1)	102	(24.6)	277	(23.0)
45–54	17	(6.3)	50	(9.6)	54	(13.0)	121	(10.0)
55-	11	(4.1)	19	(3.6)	25	(6.0)	55	(4.6)
BMI (%)								
Underweight (–18.5)	6	(2.2)	3	(0.6)	3	(0.7)	12	(1.0)
Normal (18.5–25.0)	67	(24.7)	103	(19.8)	83	(20.0)	253	(21.0)
Overweight (25.0–30.0)	29	(10.7)	41	(7.9)	62	(15.0)	132	(10.9)
Obese (30.0–)	5	(1.8)	13	(2.5)	24	(5.8)	42	(3.5)
N/A	164	(60.5)	361	(69.3)	242	(58.5)	767	(63.6)
Smoking habits (%)								
Never	55	(20.3)	101	(19.4)	109	(26.3)	265	(22.0)
<10 g/day	14	(5.2)	14	(2.7)	18	(4.3)	46	(3.8)
10–19 g/day	36	(13.3)	52	(10.0)	35	(8.5)	123	(10.2)
20– g/day	28	(10.3)	60	(11.5)	38	(9.2)	126	(10.4)
Smoker, unknown number	1	(0.4)	4	(0.8)	4	(1.0)	9	(0.7)
Former smoker	1	(0.4)	8	(1.5)	8	(1.9)	17	(1.4)
N/A	136	(50.2)	282	(54.1)	202	(48.8)	620	(51.4)
Histology (%)								
Seminoma	39	(14.4)	130	(25.0)	116	(28.0)	285	(23.6)
Nonseminoma	232	(85.6)	391	(75.0)	298	(72.0)	921	(76.4)
Surgery residual tumor (%)								
Yes	98	(36.2)	145	(27.8)	144	(34.8)	387	(32.1)
No	173	(63.8)	376	(72.2)	270	(65.2)	819	(67.9)
IGCCCG prognostic group (%)								
Good	203	(76.3)	394	(77.0)	322	(80.7)	919	(78.1)
Intermediate	45	(16.9)	89	(17.4)	53	(13.3)	187	(15.9)
Poor	18	(6.8)	29	(5.7)	24	(6.0)	71	(6.0)
CKD stage before treatment (%)								
I	238	(87.8)	466	(89.4)	360	(87.0)	1064	(88.2)
II	29	(10.7)	48	(9.2)	49	(11.8)	126	(10.4)
III	4	(1.5)	7	(1.3)	5	(1.2)	16	(1.3)
Treatment cycles (%)								
3	3	(1.1)	36	(6.9)	278	(67.1)	317	(26.3)
4	193	(71.2)	442	(84.8)	122	(29.5)	757	(62.8)
5–/high dose	75	(27.7)	43	(8.3)	14	(3.4)	132	(10.9)

N/A, not available; CKD, chronic kidney disease.

cycles, CKD stage before treatment, and a significant interaction between treatment and CKD stage. Age at treatment and secondary surgery had no influence on ΔGFR. Treatment with BEP significantly reduced renal function according to number of chemotherapy cycles (Figure 1).

For patients with normal renal function before treatment, GFR post-treatment changed −11.3% after three cycles, after four cycles −15.4% and after five cycles or more −25.9%. In patients with decreased renal function before treatment (CKD stage II or III), GFR after three cycles changed 4.3%, four cycles 0.0% and five cycles or more −12.8%.

During follow-up, there was a significant rebound in all treatment groups; however, the renal function remained subnormal in patients in CKD stage I before treatment, even when adjusting for the physiological decline in renal function in the normal population.

renal function, CVD and death

Late effects are listed in Table 2. The risk of a major cardiovascular event after 20 years was 12.7%. CKD stage III before treatment was associated with a nonsignificantly increased risk of

Figure 1. Glomerular filtration rates (GFR) based on linear mixed models. The relative GFR measured by 51Cr-EDTA clearance according to various time points. Covariates included in the model without significance: postchemotherapy surgery $P = 0.11$, Age at treatment $P = 0.62$. (A) Patients with normal renal function before treatment [chronic kidney disease (CKD) stage I or >90 ml/min/1.73 m^2]. (B) Patients with impaired renal function before treatment (CKD stage II–III or 30–90 ml/min/1.73 m^2).

later death [hazard ratio: 2.25 (0.79–6.41)], and after treatment the association was further diluted by nonsignificant associations with CVD and death (Table 3). Correspondingly ΔGFR was not associated with risks of CVD or death, neither post-treatment nor at 5 years of follow-up. The only significant covariates for later death in all models, were age and smoking.

CKD stage after treatment and number of chemotherapy cycles were compared with the background population with respect to the risk of major CVD or death, Table 3. In total, 93 patients died during follow-up versus an expected number of 46 [SMR: 2.03 (1.64–2.48)]. Cause of death was secondary cancer ($N = 28$), CVD ($N = 20$), and other ($N = 45$), (supplementary Table S3, available at *Annals of Oncology* online). The SHR for CVD in the whole cohort was significantly increased to 1.38 (1.22–1.55), but with no correlation to treatment intensity or CKD-stage.
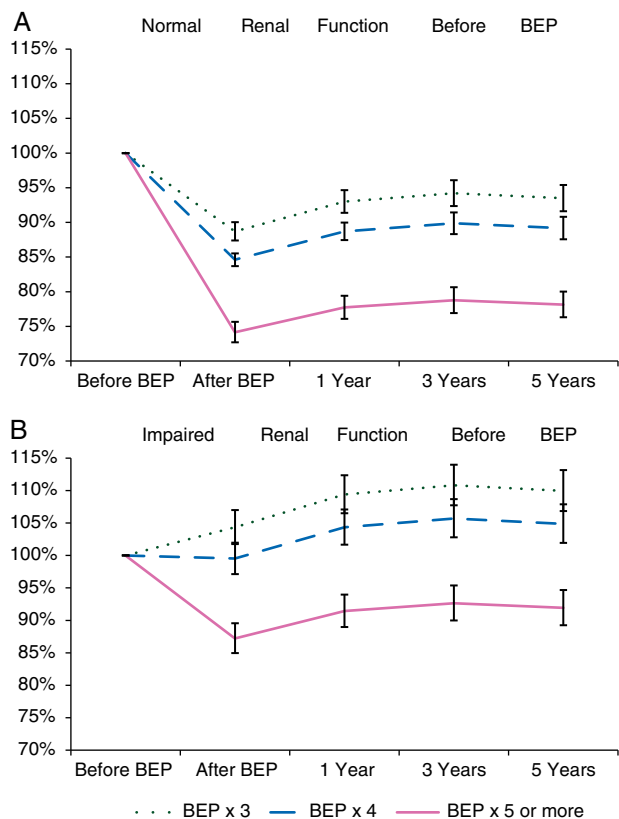
discussion

The present study includes the most comprehensive data concerning the influence of BEP treatment on renal function. All patients included were only treated with standard first-line treatment. The decrease in renal function was −11.3%, −15.4% and −25.9% after three, four or five cycles or more.

As shown in previous studies [1, 4, 5, 14], the decrease in renal function immediately after termination of chemotherapy is highly influenced by the cumulative dose of cisplatin, but, in contrast to these studies, we have documented a significant reversibility of renal function loss during follow-up. Besides, we found, that patients with impaired renal function before treatment, quite safely can receive three to four cycles of BEP with virtually no changes in GFR. In the majority of these patients, the prechemotherapy renal impairment is presumably due to mechanical obstruction from the malignant disease. Secondary surgery did not increase the risk of renal toxicity during follow-up, as only two patients needed nephrectomy. This finding is in line with Stephenson et al. who also found that only a small subset of patients undergoing postchemotherapy surgery need nephrectomy [15].

Table 2. Number of patients with any late effect or death and 20 years cumulative incidence (%) according to CKD stage after treatment

Number of patients	CKD-stage						Total	
	I		II		III		Total	
	664		406		42		1,112	
Cardiovascular disease								
Myocardial infarction (%)	19	(3.6)	22	(7.2)	3	(10.0)	45	(4.9)
Angina (%)	41	(8.6)	27	(9.5)	3	(7.3)	71	(8.6)
Cerebrovascular accident (%)	11	(2.0)	15	(4.8)	7	(21.4)	33	(3.7)
Heart failure (%)	9	(1.6)	9	(2.4)	0	(0.0)	18	(1.7)
Any above	57	(11.0)	42	(14.9)	9	(27.2)	108	(12.7)
Chronic kidney disease (%)	4	(0.7)	6	(2.2)	4	(10.8)	14	(1.6)
Death (%)	35	(6.6)	42	(11.2)	8	(18.4)	93	(9.1)

Some patients have more than one cardiovascular disease. Chronic kidney disease is defined as appearance of chronic kidney disease in a central registry.

Table 3. Hazard rates adjusted for age, time, smoking habits and postchemotherapy resection at different time points

Outcome	Covariate	Before treatment		After treatment		SHR/SMR
		P	HR (95%CI)	P	HR (95% CI)	
Death	CKD stage					
	I		1		1	1.93 (1.51–2.45)
	II	0.17	1.52 (0.84–2.73)	0.80	0.93 (0.55–1.60)	2.17 (1.30–3.38)
	III	0.09	2.40 (0.87–6.57)	0.35	1.61 (0.60–4.29)	3.43 (1.11–8.02)
	No. of cycles					
	3		1		1	1.08 (0.40–2.36)
	4	0.75	0.85 (0.31–2.32)	0.68	0.79 (0.26–2.43)	2.07 (1.61–2.62)
	5–/high dose	0.95	1.04 (0.31–3.46)	0.91	0.93 (0.24–3.51)	2.54 (1.53–3.97)
	Total					2.03 (1.64–2.48)
CVD	CKD stage					
	I		1		1	1.40 (1.23–1.60)
	II	0.36	1.31 (0.40–1.67)	0.53	0.86 (0.55–1.38)	1.12 (0.80–1.52)
	III	0.13	2.29 (0.80–6.60)	0.30	1.65 (0.63–4.32)	2.31 (1.23–3.96)
	No. of cycles					
	3		1		1	1.56 (1.07–2.19)
	4	0.57	0.81 (0.40–1.66)	0.81	0.91 (0.41–2.00)	1.40 (1.21–1.61)
	5–/high dose	0.15	0.43 (0.14–1.37)	0.28	0.52 (0.16–1.72)	1.17 (0.82–1.61)
	Total					1.38 (1.22–1.55)

The influence of ΔGFR (GFR post-treatment – GFR pretreatment, change of 10 ml/min/1.73 m^2) in the same models: Death [$P = 0.50$, HR: 1.06 (0.90–1.25)] and CVD [$P = 0.61$, HR: 0.97 (0.84–1.11)]. At 5-year follow-up, the influence of ΔGFR (GFR at 5 years – GFR pretreatment) was: Death [$P = 0.19$, HR: 0.83 (0.62–1.11)] and CVD [$P = 0.45$, HR: 0.89 (0.66–1.20)].
HR, hazard ratio; CKD stage, chronic kidney disease stage; CVD, cardiovascular disease; CI, confidence interval; SHR, standardized hospitalization rate; SMR, standardized mortality rate.

In the present study, we found an overall significantly increased risk of major CVD and death compared with the background population. These findings are in accordance with other large studies [7, 16]. A decreased pretreatment renal function was associated with a nonsignificantly increased risk of CVD, in line with large population-based studies [6, 17]. We could, however, not detect a relationship with changes in renal function during treatment and CVD despite a long median follow-up of 15 years. There are several possible explanations for the missing impact of these changes.

First, the decrease in GFR was small and therefore likely clinically insignificant. In the present study, one-third ended in CKD stage II and only 3% in stage III after treatment. In recent smaller studies based on eGFR, 10–23% of patients ended in CKD stage III during follow-up [4, 5, 18]. First-line treatments included a wide range of chemotherapy regimens and additionally a large part of patients received salvage or second-line chemotherapy (26–43%). Conversely, in a small study by Fossa et al. using mGFR, patients treated with conventional dose BEP only, experienced a long-term decline in GFR of only 10% [1], which is in line with the present results. Secondly, patients with the highest pretreatment GFR also had the highest relative change in GFR, and, consequently, these patients still have a sufficient renal function. Possibly, renal function loss in otherwise healthy adults may be of minor importance. In a study on kidney donors, no increased risk of CVD is seen in the first decade after kidney donation [19]. Additionally, during follow-up GFR normalize in a large proportion of our cohort. A recent study employing eGFR [18] describe a continuous decrease of

renal function after treatment has ceased. This is likely caused by imprecision of the estimates used [20].

It seems that, even a few cycles of BEP increases the risk of CVD and we could not detect a significant difference with three or four cycles of cisplatin and later risk of CVD or death. The body of patients receiving small or large cumulative doses of cisplatin was relatively modest due to exclusion of patients with relapse and second-/third-line treatment and the nonuse of one or two cycles of adjuvant BEP in patients with stage I nonseminoma. Also we did not include patients who did not receive BEP. However, patients on surveillance have normal renal function during follow-up and do not experience an increased risk of CVD [1, 7, 16].

We have looked at a large, unselected cohort of GCC-patients with a long follow-up. Due to the time-span and retrospective nature of the cohort, some limitations must be considered. There were missing values in important confounders, leading to the use of imputational methods. If the confounders were omitted from analyses (results not shown), no changes in the results were noted, strengthening the interpretation of the results. Treatment and registration habits in the national registers changed slightly over time. Three cycles of chemotherapy to the good prognosis group were introduced in 2001 implying short median follow-up for patients with only three cycles of BEP and the evaluation of late effects for this group might be too early. A missing association of renal impairment and CVD can be caused by a type II error, if the cohort has been too small to show. However, we did find a significantly increased risk of CVD and death in patients treated with chemotherapy, and the

results did not in any way favor a trend towards an association between renal function loss and risk of late effects.

Cisplatin-based combination chemotherapy induces significant deteriorations in renal function. These changes are not associated with an increased risk of late CVD or death. However, we confirm that treatment with chemotherapy in itself causes a risk, and that patients with impaired renal function before treatment have an additionally increased risk. The latter patient group needs close follow-up concerning cardiovascular risk factors.

references

1. Fossa SD, Aass N, Winderen M et al. Long-term renal function after treatment for malignant germ-cell tumours. Ann Oncol 2002; 13: 222–228.

2. Osanto S, Bukman A, Van HF et al. Long-term effects of chemotherapy in patients with testicular cancer. J Clin Oncol 1992; 10: 574–579.

3. Daugaard G, Rossing N, Rorth M. Effects of cisplatin on different measures of glomerular function in the human kidney with special emphasis on high-dose. Cancer Chemother Pharmacol 1988; 21: 163–167.

4. Suer E, Mermerkaya M, Gulpinar O et al. Does the number of cycles of cisplatin based chemotherapy have any effect on renal function in patients with testicular germ cell tumor? J Urol 2013; 190: 2081–2085.

5. Cost NG, Adibi M, Lubahn JD et al. Effect of testicular germ cell tumor therapy on renal function. Urology 2012; 80: 641–648.

6. Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296–1305.

7. van den Belt-Dusebout AW, Nuver J, de Wit R et al. Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 2006; 24: 467–475.

8. Groth S, Aasted M. 51Cr-EDTA clearance determined by one plasma sample. Clin Physiol 1981; 1: 417–425.

9. Levey AS, Coresh J, Balk E et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003; 139: 137–147.

10. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011; 39: 22–25.

11. Andersen TF, Madsen M, Jorgensen J et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46: 263–268.

12. Juel K, Helweg-Larsen K. The Danish registers of causes of death. Dan Med Bull 1999; 46: 354–357.

13. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009; 9: 57.

14. Aass N, Fossa SD, Aas M, Lindegaard MW. Renal function related to different treatment modalities for malignant germ cell tumours. Br J Cancer 1990; 62: 842–846.

15. Stephenson AJ, Tal R, Sheinfeld J. Adjunctive nephrectomy at post-chemotherapy retroperitoneal lymph node dissection for nonseminomatous germ cell testicular cancer. J Urol 2006; 176: 1996–1999; discussion 1999.

16. Haugnes HS, Wethal T, Aass N et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 2010; 28: 4649–4657.

17. Di Angelantonio E, Chowdhury R, Sarwar N et al. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ 2010; 341: c4986.

18. Inai H, Kawai K, Ikeda A et al. Risk factors for chronic kidney disease after chemotherapy for testicular cancer. Int J Urol 2013; 20: 716–722.

19. Garg AX, Meirambayeva A, Huang A et al. Cardiovascular disease in kidney donors: matched cohort study. BMJ 2012; 344: e1203.

20. Lauritsen J, Gundgaard MG, Mortensen MS et al. Reliability of estimated glomerular filtration rate in patients treated with platinum containing therapy. Int J Cancer 2014; 135: 1733–1739.