ORIGINAL ARTICLE

Suspected Infertility After Treatment for Leukemia and Solid Tumors in Childhood and Adolescence

Magdalena Balcerek, Simone Reinmuth, Cynthia Hohmann, Thomas Keil, Anja Borgmann-Staudt

SUMMARY

Background: With improved cure rates of cancer in children and adolescents, the long-term effects of oncological treatment, including impaired fertility, have become an important clinical issue.

Methods: In 2008, we conducted a nationwide survey in Germany in which we asked 4689 female and male patients who had been treated for cancer in childhood or adolescence for information on menstruation, previous fertility testing (if any), attempts to conceive, and pregnancies. In a complementary study carried out in 2009, 748 former cancer patients in Berlin were offered hormone testing and sperm analysis. The defined criteria for suspected infertility were, in women, anti-muellerian hormone levels below 0.1 ng/mL; in men, FSH levels above 10 IU/L and inhibin B levels below 80 pg/mL, or azoospermia.

Results: The respondents to the nationwide survey included 1476 leukemia survivors and 1278 persons who had had a solid tumor. 104 former leukemia patients and 96 former solid tumor patients had already undergone fertility testing, leading to the suspicion of infertility in 26% and 34% of the persons in these respective groups (95% confidence intervals [CI], 18%–34% and 25%–43%). The patients who were tested in the Berlin study included 59 leukemia survivors and 104 persons who had had a solid tumor. The frequency of suspected infertility in these two groups was 25% and 27%, respectively (95% CI, 14%–36% and 18%–36%).

Conclusion: Up to one-third of adults who undergo fertility testing after having been treated for cancer in childhood or adolescence have suspected infertility. Patients and their parents should be counseled about the possibility of infertility and about fertility-preserving measures.

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Optimization of treatment over the course of the past 30 years has improved the survival rate of children with malignant disease. The 5-year survival rate in children under 15 with cancer has increased from 67% at the beginning of the 1980s to 83% today (1).

Ninety percent of the long-term survivors of both sexes who responded to a nationwide German survey in 2008 wanted children (Borgmann-Staudt A, et al.: *Pediatr Blood Cancer* 2009; 53: 857; abstract), the same proportion as in the corresponding age group of the general population (2, e1). However, some former pediatric oncology patients are not able to fulfill this wish because their gonads have been damaged by chemotherapy and/or radiotherapy (Borgmann-Staudt A, et al.: *Pediatr Blood Cancer* 2009; 53: 857; abstract, [3]).

Around 5% of couples in the general population are infertile (4). Infertility rates of 3% in 25-year-olds and 6% in 30-year-olds have been described (5). The rate seems to be considerably higher, however, in survivors of cancer in childhood or adolescence. Even women with initially regular menstrual bleeding after treatment have a limited chance of conception, because premature ovarian failure may lead to early exhaustion of the supply of ova (6, 7). Depending on age and type of treatment, up to one third of female patients may be affected (6–8).

To find out more about the frequency of and risk factors for infertility in pediatric oncology patients, we carried out a nationwide survey of former patients in 2008. This inquiry, “Fertility after chemotherapy and radiotherapy in children and adolescents, FeCt,” was conducted in cooperation with the German Childhood Cancer Registry (GCCR) (Borgmann-Staudt A, et al.: *Pediatr Blood Cancer* 2009; 53: 857; abstract, [9]). In an effort to substantiate the results of the survey we performed a supplementary study in 2009, offering hormone testing and sperm analysis to former cancer patients in Berlin (7).

In this article we evaluate some of the findings from both the nationwide survey and the Berlin hormone testing and sperm analysis study. We present the data on the frequency of pregnancy and of suspected

Department of Pediatrics, Division of Oncology and Hematology, Charité Berlin: Balcerek, Reinmuth, PD Dr. med. Borgmann-Staudt

Institute for Social Medicine, Epidemiology, and Health Economics, Charité Berlin: Dipl.-Psych. Hohmann, PD Dr. med. Keil

infertility in survivors of leukemia and solid tumors in childhood and adolescence. A further analysis, not described here, presents the risk factors for infertility after treatment for cancer.

Methods

Nationwide survey

Study design and participants—The methods have already been described in detail (Borgmann-Staudt A, et al.: *Pediatr Blood Cancer* 2009; 53: 857; abstract, [9]). In 2008 we conducted a survey of fertility in almost all of the adult long-term survivors of cancer in childhood or adolescence registered in the GCCR. We excluded patients with Hodgkin lymphoma, because the gonadotoxicity of the treatment protocols used for this disease has already been described (3, 10), and patients with stem cell transplantation, who are known to have a high infertility rate (11, 12). Furthermore, patients with a recurrence or a second primary malignancy were excluded because of the difficulty in reliably establishing the cumulative doses of chemotherapy and radiotherapy. The nationwide survey was approved by the ethics committee of Charité–Universitätsmedizin Berlin.

Determination of reduced fertility—The following data on the participants in the nationwide survey were used to determine the presence of reduced fertility:

- Menstrual history
- Previous investigations of fertility
- Attempts to conceive
- Pregnancies
- Births.

The German-language questionnaire used in the survey can be found at http://paedonko.charite.de/en/research/fertility_after_chemotherapy.

Berlin hormone testing and sperm analysis study

Study design and participants—The methods have already been described in detail (7). In 2009, following the nationwide survey, we offered hormone testing and sperm analysis to former pediatric oncology patients, treated in Berlin, who had since attained adulthood. In addition, the same questionnaire as in the nationwide survey was used again. No underlying malignant diseases were excluded; in contrast to the nationwide survey, patients with Hodgkin lymphoma and patients post stem-cell transplantation were included. However, recurrences and second primary tumors were again grounds for exclusion. The hormone testing and sperm analysis study was approved by the ethics committee of Charité–Universitätsmedizin Berlin.

Determination of reduced fertility—The following data were used to determine the presence of reduced fertility:

- In women we measured the level of anti-müllerian hormone (AMH), which correlates well with the follicular reserve (13). AMH levels <0.1 ng/mL were interpreted as “suspected infertility,” concentrations in the range ≥0.1 ng/mL to <1.0 ng/mL as “suspected impending infertility” (14).

FIGURE 1

Distribution of diagnoses among the 2754 responders to the nationwide FeCt survey in 2008 (leukemia n = 1476, solid tumor n = 1278) compared to the non-responders.

Leukemia: acute lymphoblastic leukemia, acute myeloblastic leukemia; solid tumor: non-Hodgkin lymphoma, Ewing sarcoma, osteosarcoma, soft tissue sarcoma, extra-/intracranial germ cell tumor, brain tumor, neuroblastoma, hepatic and renal tumor, others

- The criterion for suspected infertility in men was a follicle-stimulating hormone (FSH) level >10 IU/L together with an inhibin B level <80 pg/mL; this combination correlates well with spermiogenesis (15).
- Azoospermia was also rated as suspected infertility. The spermiograms were performed and interpreted according to the current WHO guidelines (16).

Results

Nationwide survey

The questionnaire was sent to 4689 former pediatric oncology patients and completed by 2754 of them, a response rate of 59%. The responders and non-responders were of comparable age both at the time of diagnosis and when the survey was conducted (9).

The responders included 1476 former leukemia patients with a median age of 7 years (range 0 to 15 years) at diagnosis and 25 years (19 to 43 years) at the time of the survey. The 1278 patients treated for a solid tumor had a median age of 10 years (0 to 15 years) at diagnosis and 24 years (19 to 43 years) at the time of the survey. The distribution of pediatric oncology diagnosis groups was similar in responders and non-responders (Figure 1).

TABLE

Participants reporting pregnancy and participants with abnormal fertility test results^{*1}

FeCt participants		At least one pregnancy reported, % (n/N)	Suspected infertility, % (n/N)
Leukemia	Total	19% (272/1458) ^{*2}	26% (27/104) ^{*3}
	ALL, CoALL	18% (237/1302)	26% (23/90)
	AML	22% (35/156)	29% (4/14)
Solid tumor	Total	16% (195/1253) ^{*2}	34% (33/96) ^{*3}
	NHL	33% (27/82)	29% (2/7)
	Ewing	15% (17/112)	43% (6/14)
	COSS	19% (29/153)	31% (5/16)
	CWS	18% (42/228)	40% (6/15)
	MAHO, MAKEI	14% (19/134)	50% (4/8)
	NB	13% (8/61)	67% (2/3)
	SIOP, WTS	16% (34/211)	28% (5/18)
	HB	-% (-/-)	-% (-/-)
	HIT	4.3% (9/207)	13% (1/8)
	GCT	12% (3/25)	20% (1/5)
	Others	22% (7/32)	50% (1/2)

^{*1} Therapy optimization studies: ALL, CoALL: for treatment of patients with acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; NHL: non-Hodgkin lymphoma; Ewing: Ewing sarcoma; COSS: osteosarcoma; CWS: soft-tissue sarcoma; MAHO, MAKEI: extracranial germ cell tumors; NB: neuroblastoma; SIOP, WTS: nephroblastoma; HB: hepatoblastoma; HIT: brain tumors; GCT: intracranial germ cell tumor, in the patient groups of the responders to the nationwide survey in 2008 who were treated according to their diagnosis after therapy optimization studies had been performed.

^{*2} Pregnancies in participants with leukemia versus solid tumor: 19% vs. 16%, $p = 0.033$

^{*3} Suspected infertility (according to results of fertility tests) in participants with leukemia versus solid tumor: 26% vs. 34%, $p = 0.195$

Pregnancies—Among the former leukemia patients, 19% (272/1458) of the female and male responders reported at least one pregnancy or insemination leading to pregnancy. Of the responders who had been treated for a solid tumor in childhood or adolescence, 16% (195/1253) reported at least one pregnancy ($p = 0.033$).

Suspected infertility—Altogether, 551 (37.3%) women with leukemia and 507 (39.7%) women with a solid tumor answered questions about menstruation. Among those formerly treated for leukemia, 43 (7.8%) reported temporary amenorrhea and 8 (1.5%) reported permanent amenorrhea. In those formerly treated for solid tumors, the corresponding figures were 69 (13.6%) and 30 (5.9%) respectively.

Fifty-five responders with former leukemia and 45 with a former solid tumor gave answers to the question “Have you tried to conceive a child?” that could be evaluated for correspondence with the WHO definition of infertility (no pregnancy despite unprotected sexual intercourse over a period of two years [17]). Twenty (36.4%) of those treated for leukemia and 23 (51.1%)

of those treated for solid tumors reported that they had spent at least 24 months unsuccessfully trying to conceive a child with a partner who was not known to be infertile.

Investigations of fertility were reported by 104 responders with leukemia and 96 responders with a solid tumor; infertility was suspected in 26% (27/104) and 34% (33/96) respectively (Table). Those who had undergone fertility testing were older than those who had not: median 10.0 versus 8.0 years at the time of diagnosis ($p < 0.001$), 27.5 versus 24.0 years when surveyed ($p < 0.001$). The distribution of diagnoses in the responders whose fertility had been investigated matched that in the responders as a whole.

Berlin hormone testing and sperm analysis study

We mailed questionnaires to 748 former pediatric oncology patients who had been treated in Berlin; 163 of them (22%) agreed to take part in the study and completed the questionnaire. Of these former patients, 159 underwent hormone testing and 42, sperm analysis. The distribution of diagnoses among the responders was roughly comparable with the GCCR data for the German pediatric oncology population in 2007 (Figure 2).

Fifty-nine former leukemia patients and 104 who had been treated for a solid tumor took part in the study. Eight of the 59 leukemia patients and one of the 104 with a solid tumor had undergone stem cell transplantation during the course of their oncological treatment. The median age of the leukemia patients was 9 years (0 to 17 years) at diagnosis and 22 years (19 to 42 years) at the time of the survey. The responders with a solid tumor had a median age of 12 years (0 to 34 years) at diagnosis and 24 years (19 to 41 years) at the time of the survey.

Pregnancies—Twelve (7%) responders, three former leukemia patients and nine with a solid tumor, reported at least one pregnancy.

Suspected infertility—Among the 59 responders with leukemia, 15 (25%) were found to fulfill at least one criterion of infertility on hormone testing and sperm analysis and were therefore classified as having suspected infertility. These 15 responders included 11 (33%) of 33 men. In 9 (29%) of 31 men infertility was suspected on the basis of hormone analysis, and in 3 (18%) of 17 the spermiogram revealed azoospermia. In 4 (15%) of 26 women treated for leukemia in childhood or adolescence, suspected infertility was indicated by hormone analysis. Furthermore, suspected impending infertility was identified in 1 (4%) of the female former leukemia patients.

In the group of former patients with solid tumors, 28 (27%) of the 104 responders fulfilled at least one criterion of infertility and were categorized as having suspected infertility. Hormone testing and sperm analysis showed suspected infertility in 18 (41%) of 44 men: in 15 of 42 men it was the results of hormone testing that led to this classification, and in 10 of 25 men sperm analysis indicated azoospermia. Hormone testing

pointed to suspected infertility in 10 (17%) of 60 women treated for a solid tumor in childhood or adolescence, and 20 (33%) of 60 were rated as having suspected impending infertility.

Discussion

Principal findings

Impairment of fertility represents a significant problem for former pediatric oncology patients. The findings of the nationwide survey in 2008 and the Berlin hormone testing and sperm analysis study in 2009 were comparable with regard to loss of fertility. However, the frequency of suspected infertility differed between the two diagnosis groups. Among the responders to the nationwide study who had undergone fertility testing, former leukemia patients tended to have a lower rate of abnormal results than those treated for a solid tumor (26% versus 34%). In the Berlin hormone testing and sperm analysis study, 25% of the former leukemia patients and 27% of the former solid tumor patients fell into the category of suspected infertility.

In the nationwide survey the group of former leukemia patients had a pregnancy rate of 19%, significantly higher than that among those with a solid tumor (16%). The pregnancy rate among the responders to the nationwide survey as a whole was significantly lower than in the same age segment of the German general population (9, 18).

Comparison with other studies

It is not surprising that former leukemia patients have a lower risk of infertility than former patients with a solid tumor, because the latter form a higher proportion of postpubertal cancer patients and more often undergo irradiation of the pelvic region. Treatment after puberty and pelvic irradiation were significant risk factors for impaired fertility in the Berlin hormone testing and sperm analysis study (7, e2). We are currently analyzing the data from the nationwide survey in more detail to establish the risk factors for reduction in fertility.

Green et al. investigated the effect of pediatric oncology treatment on ovarian function in the cohort of the Childhood Cancer Survivor Study. Acute ovarian failure occurred in 6.3% of the female participants, with irradiation of the pelvis, administration of alkylating agents including procarbazine, and higher age at the time of diagnosis emerging as significant risk factors. Moreover, 8% of the female participants experienced premature menopause; the risk factors were higher age, higher ovarian radiation dose, increasing alkylating agent score, and Hodgkin lymphoma as underlying disease. Patients with a tumor or radiation dose >30 Gy in the region of the hypothalamus and/or the hypophysis were excluded from this study (19).

The three factors repeatedly described as increasing the risk of infertility (7, 8, 19, 20) are:

- Administration of alkylating agents
- Irradiation of the pelvis
- Treatment after puberty.

FIGURE 2

Distribution of diagnoses among the 163 participants in the Berlin hormone testing and sperm analysis study in 2009 (leukemia n = 59, solid tumor n = 104) compared with the patients listed in the German Childhood Cancer Registry (GCCR) in 2007.

Leukemia: lymphoblastic leukemia, acute myeloblastic leukemia; solid tumor: Hodgkin lymphoma, non-Hodgkin lymphoma, Ewing sarcoma, osteosarcoma, soft tissue sarcoma, extra-/intracranial germ cell tumor, brain tumor, neuroblastoma, hepatic and renal tumor, others

Strengths and limitations

Our survey in 2008, with a response rate approaching 60%, is the first large nationwide study of fertility after chemotherapy and radiotherapy in childhood and adolescence to be carried out in Germany. The participants in this study were all treated according to the protocols of the Society for Paediatric Oncology and Haematology, which are employed principally in the German-speaking countries. The median ages of the study collectives at the time of inquiry were relatively low in both the nationwide survey and the Berlin hormone testing and sperm analysis study, at 26 and 23 years respectively. This is largely explained by the fact that the participants were recruited from the GCCR, whose systematic registration and regular updating of data on pediatric oncology patients in Germany did not begin until 1980 (e2). It cannot be excluded that fertility testing had been carried out above all in study participants who suspected infertility: only 200 of the 2754 responders to the nationwide survey reported previous investigation of fertility. Those whose fertility had been tested were 2 years older at diagnosis and 3.5 years older at the time of the survey than those who had not had their fertility tested. However, the distribution of

oncological diagnoses in the responders with fertility testing was comparable to that in all responders.

In view of the lower response rate (22%), it also cannot be excluded that above all patients who suspected they might be infertile took part in the Berlin hormone testing and sperm analysis study. The proportion of patients with elevated risk to fertility may also be higher in the Berlin hormone testing and sperm analysis study than in the nationwide survey because it included nine former recipients of stem cell transplantation, which is known to increase the danger of infertility (20). In comparison with the distribution of pediatric oncology diagnoses in the general population, the participants in the Berlin hormone testing and sperm analysis study included a higher proportion of patients with Hodgkin lymphoma and a lower proportion of brain tumor patients (7). Patients with Hodgkin lymphoma have a proven elevated risk of infertility because of the possible irradiation of lymph nodes, including those in the pelvis, and because of treatment with procarbazine (3, 13).

Conclusions

Up to one third of the subgroup of patients with fertility testing fell into the category of suspected infertility, compared with an infertility rate of around 5% in the corresponding age segment of the general population (4, 5). Even when interpreting the findings cautiously owing to the possibility of selection bias, the necessity for comprehensive explanation of the potential for measures to preserve fertility—particularly in patients with known risk factors such as pelvic irradiation and treatment after puberty—is quite clear. Because the patients have often not reached puberty and because treatment cannot be postponed, fertility-preserving measures are frequently limited to the following (21–25):

- Cryopreservation of sperm and testicular tissue
- Ovariopexy
- Cryopreservation of oocytes and—not yet established—of ovarian tissue

Further information on protection of fertility can be found at www.fertiprotekt.de.

KEY MESSAGES

- The studies revealed suspected infertility in up to one third of the subgroup of former pediatric oncology patients who underwent fertility testing (7%, n = 200).
- The pregnancy rate was higher in former leukemia patients than in those who had had a solid tumor.
- Given the high rate of impaired fertility in former pediatric oncology patients, comprehensive explanation of the risk of infertility and the corresponding fertility-preserving measures to patients and their parents is essential.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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Corresponding author

PD Dr. med. Anja Borgmann-Staudt
 Charité – Universitätsmedizin Berlin
 Campus Virchow-Klinikum
 Otto-Heubner-Centrum für Kinder- und Jugendmedizin
 Klinik für Pädiatrie m. S. Onkologie/Hämatologie
 Augustenburger Platz 1, 13353 Berlin, Germany
anja.borgmann@charite.de

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eBOX

Statistical Methods

The master data—including information on underlying disease—of the participants in the nationwide survey and the Berlin hormone testing and sperm analysis study were provided by the German Childhood Cancer Registry on presentation of the participants' signed consent. For analysis the patients were divided by their diagnosis and the corresponding treatment protocols into the following two groups:

- Leukemia:
 - acute lymphoblastic leukemia (ALL)
 - acute myeloblastic leukemia (AML)
- Solid tumor:
 - non-Hodgkin lymphoma (NHL)
 - Ewing sarcoma
 - osteosarcoma
 - soft tissue sarcoma
 - extra-/intracranial germ cell tumor
 - brain tumor
 - neuroblastoma
 - hepatic and renal tumor
 - others

For analysis of the data from the Berlin hormone testing and sperm analysis study, the group of solid tumors also included Hodgkin lymphoma.

Predictive Analytics Software version 18 was used for statistical analysis. Frequencies and median values were calculated as descriptive statistics. The chi-square test was used for comparison of the two diagnosis groups with regard to the variable “suspected infertility.”