Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG)

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To date, there is little information on the impact of more aggressive treatment regimen such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) on the fertility of male patients with Hodgkin lymphoma (HL). We evaluated the impact of BEACOPP regimen on fertility status in 38 male patients with advanced-stage HL enrolled into trials of the German Hodgkin Study Group (GHSG). Before treatment, 6 (23%) patients had normozoospermia and 20 (77%) patients had dysspermia. After treatment, 34 (89%) patients had azoospermia, 4 (11%) had other dysspermia, and no patients had normozoospermia. There was no difference in azoospermia rate between patients treated with BEACOPP baseline and those given BEACOPP escalated (93% vs 87%, respectively; *P* > .999). After treatment, most of patients (93%) had abnormal values of follicle-stimulating hormone, whereas the number of patients with abnormal levels of testosterone and luteinizing hormone was less pronounced—57% and 21%, respectively. In univariate analysis, none of the evaluated risk factors (ie, age, clinical stage, elevated erythrocyte sedimentation rate, B symptoms, large mediastinal mass, extranodal disease, and 3 or more lymph nodes) was statistically significant. Male patients with HL are at high risk of infertility after treatment with BEACOPP. (Blood. 2008;111:71-76)

Introduction

The prognosis of patients with Hodgkin lymphoma (HL) has improved substantially over the last decades. Depending on the stage of disease and risk factors, more than 80% of patients can be cured.[1-3] Since most patients with HL are young, with a mean age of 32 years,[4] long-term side effects of treatment increasingly skip scientific interest. Patients with HL are at higher risk for secondary malignancies such as acute myeloid leukemia, non-Hodgkin lymphoma, and solid tumors.[5-9] Other late effects include pulmonary and cardiac complications[10,11] and infertility[12-14]

Infertility after treatment particularly presents a high psychosocial burden for young patients. A recent report revealed that 51% of men with cancer expressed their wish to preserve their capacity for procreation in the future, including 77% of men who were still childless when their cancer was diagnosed.[15] Several studies have investigated the fertility status in male patients with HL. Chemotherapy regimens, which include alkylating agents such as cyclophosphamide and procarbazine, were particularly associated with infertility.[16,17] Interestingly, most male patients with HL were shown to have inadequate sperm quality even before treatment.[18] The issue of female fertility among patients with HL after treatment with a new BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen was recently analyzed and showed that after a median follow-up of 3.2 years, 51.4% of women receiving 8 cycles of BEACOPP escalated had continuous amenorrhea. Amenorrhea was significantly more frequent after BEACOPP escalated compared with COPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine) or BEACOPP baseline ($P = .007$).[13] To date, there is still very little information on the fertility of male patients with HL undergoing treatment with BEACOPP.

The present study investigates the impact of chemotherapy with BEACOPP on fertility status in male patients with advanced HL treated within prospectively randomized trials of the German Hodgkin Study Group (GHSG; see Document S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article). Fertility status was correlated with clinical and biological features at the time of diagnosis as well as with the treatment received.

Methods

Patient selection and study design

We evaluated male patients with HL who had completed fertility analysis after treatment with the BEACOPP regimen. All patients had a histologically confirmed first diagnosis of HL by the GHSG expert pathologists panel and were enrolled into the clinical trails HD9 (arms B and C) and HD12 (arms A, B, C, and D) between 1994 and 2002. The design of the 2 trials, including the treatment given is shown in Tables 1 and 2. If not otherwise indicated, BEACOPP included all variants of schedule as BEACOPP baseline and BEACOPP escalated. Eligibility criteria at study entry included adequate organ function as defined by: a creatinine clearance greater than 60 mL/minute, serum transaminases less than 3 times that of normal, and bilirubin less than 2 mL/dL, left ventricular ejection fraction more than 0.45, forced expiratory volume in first-second or diffusion capacity of carbon monoxide greater than 60% of predicted, and a

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Table 1. Patient treatment

Treatment protocol	Patients (n = 38)
HD9 (1994-1998)	
Arm A (4 × COPP/ABVD + RT-IF*)	0
Arm B (8 × BEACOPP baseline + RT-IF*)	15
Arm C (8 × BEACOPP escalated + RT-IF*)	18
Total	33
HD12 (1998-2002)	
Arm A (4 × BEACOPP escalated + 4 × BEACOPP escalated + RT-IF*)	1
Arm B (4 × BEACOPP escalated + 4 × BEACOPP escalated)	2
Arm C (4 × BEACOPP escalated + 4 × BEACOPP baseline + RT-IF*)	1
Arm D (4 × BEACOPP escalated + 4 × BEACOPP baseline)	1
Total	5

Data are numbers of patients. RT-IF indicates involved field radiotherapy; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; and COPP/ABVD, cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine.

*RT-IF on bulk/residual mass.

Karnofsky performance score higher than 60, as well as white blood cell (WBC) counts greater than 3.5×10^9/L (3500/μL), hemoglobin level greater than 80 g/L (8.0 g/dL), and platelet counts greater than 100×10^9/L (100 000/μL). In addition, a negative HIV test and absence of active infection were also required. For the fertility analysis, the age of patients was restricted to younger than 60 years. These studies were approved by the institutional review board of the University of Cologne. Informed consent was obtained in accordance with the Declaration of Helsinki. Patients whose fertility status was assessed after the end of the treatment had to be free of HL.

Semen analysis

The semen samples were evaluated for sperm volume, sperm count, sperm forward motility, and morphologic criteria of spermatozoa according to World Heath Organization (WHO) guidelines.[19] The nomenclature of pathologic patterns of ejaculate followed Eliasson's classification of dysspermia.[20] Conditions of disturbed sperm quality included oligozoospermia (ie, sperm concentration of 10^6/mL to 20×10^6/mL), cryptozoospermia (ie, sperm concentration less than 10^6/mL), asthenozoospermia (ie, sperm with forward motility of less than 50%) and teratozoospermia (ie, sperm with normal morphology of less than 30%). Combined severe damages were defined as OAT syndrome (disturbance of all 3 variables), or azoospermia (ie, the complete absence of spermatozoa in ejaculate). Before the collection of sperm samples, all patients underwent a physical examination in order to evaluate testicular volume, the presence of varicocele, a history of cryptorchidism, or inflammation of the seminal tract.

Table 2. Drugs and schedules used

Treatment protocol	Dose, mg/m²	Route	Schedule
Treatment regimen for BEACOPP baseline			
Bleomycin	10	IV	Day 8
Etoposide	100	IV	Days 1-3
Doxorubicin	25	IV	Day 1
Cyclophosphamide	650	IV	Day 1
Vincristine	1.4; max, 2 mg	IV	Day 8
Procarbazine	100	PO	Days 1-7
Prednisone	40	PO	Days 1-14
Treatment regimen for BEACOPP escalated			
Bleomycin	10	IV	Day 8
Etoposide	200	IV	Days 1-3
Doxorubicin	35	IV	Day 1
Cyclophosphamide	1250	IV	Day 1
Vincristine	1.4; max, 2 mg	IV	Day 8
Procarbazine	100	PO	Days 1-7
Prednisone	40	PO	Days 1-14

Both regimens repeat on day 22.
IV indicates intravenously; and PO, orally.

Hormone analysis

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were measured by commercial radioimmune assays (RIAs). Normal laboratory ranges are as follows: FSH, 1 to 7 U/L; LH, 2 to 10 U/L; and testosterone, 3.5 to 8.6 μg/L.

Statistical analysis

Demographics and disease characteristics were summarized using descriptive statistics. Fisher exact test, Wilcoxon rank-sum test, and signed-rank test were used to investigate differences on proportions and means, respectively. Relations between the different variables and fertility status were evaluated by logistic regression analysis. Variables tested were age, clinical stage, elevated erythrocyte sedimentation rate, B symptoms, large mediastinal mass, extranodal disease and 3 or more lymph nodes. Statistical analysis was performed with SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Patient characteristics

The fertility status was available in 38 patients; 33 patients were treated within the HD9 study and 5 were treated within the HD12 study. There were 593 male patients younger than 60 years in the HD9 trial (arms B and C) and 953 patients younger than 60 years in the HD12 trial. The very small number of evaluated patients with fertility status reflects the difficulties in recruitment of patients for sperm assessment; however, this analysis is still the most comprehensive in terms of patient treated with BEACOPP. The median age was 26 years (range, 16-41 years); most patients were in clinical stage III (22 patients; 58%), followed by the group of patients in stage II B with risk factors (large mediastinal mass, extranodal disease; 11 patients; 29%) and patients in stage IV (5 patients; 13%). There was no significant difference between the group treated with BEACOPP baseline and BEACOPP escalated in terms of patient characteristics (Table 3). A total of 23 (61%) patients were given 8 cycles of BEACOPP escalated (including 2 patients treated with 4 cycles of BEACOPP escalated followed by 4 cycles of BEACOPP baseline), and 15 (39%) patients received 8 cycles of BEACOPP baseline. A total of 32 (84%) patients received radiotherapy after chemotherapy, with 3 patients receiving infradiaphragmal radiation. Among the patients treated with infradiaphragmal radiotherapy, the radiation field included spleen (40 Gy), spleen hilus (40 Gy), and para-aortal nodes (40 Gy) in 1 patient. In the second patient, iliac nodes (right), inguinal nodes (right), and femoral nodes (right) were irradiated with 20 Gy each. The third patient received radiation on the spleen (39 Gy), spleen hilus (39 Gy), para-aortal nodes (39 Gy), and iliac nodes on both sides (39 Gy).

Semen analysis

From 38 patients enrolled in this study, 26 patients were examined before and after treatment, and 12 patients were examined after treatment only. Using logistic regression analysis, we observed no significant influence of the pretreatment fertility status on the posttreatment fertility status (n = 26; $P = .659$). Therefore, we decided to perform the further evaluation on all 38 patients.

Table 3. Patient characteristics

Patient characteristics	Total, n = 38	BEACOPP baseline, n = 15	BEACOPP escalated, n = 23	*P*
Median age, y (range)	26 (16-41)	26 (18-35)	26 (16-41)	.511*
Ann Arbor stage, no. (%)				
II B and risk factors†	11 (29)	4 (27)	7 (30)	
III	22 (58)	9 (60)	13 (57)	
IV	5 (13)	2 (13)	3 (13)	> .999
Risk factors, no. (%)				
ESR 30 or more	20 (53)	6 (40)	14 (61)	.320‡
B symptoms	24 (63)	8 (53)	16 (70)	.492‡
Large mediastinal mass	15 (39)	5 (33)	10 (43)	.736‡
Extranodal disease	7 (18)	2 (13)	5 (22)	.681‡
3 or more lymph node areas involved	33 (87)	12 (80)	21 (91)	.365‡
Radiotherapy	32 (84)	13 (87)	19 (83)	>.999
Radiotherapy infradiaphragmal	3 (8)	1 (7)	2 (9)	>.999

ESR indicates erythrocyte sedimentation rate.
*Wilcoxon rank-sum test.
†Risk factors indicate large mediastinal mass and extranodal disease.
‡Fisher exact test.

Of the 38 patients analyzed after treatment, 25 (66%) patients were analyzed once, 11 (29%) were analyzed twice, and 2 (5%) patients had multiple analyses. The median sperm concentration was 0.0×10^6/mL (mean, 0.9×10^6/mL; range, 0.0-32.4 $\times 10^6$/mL). Most patients (34; 89%) had azoospermia, with 4 (11%) patients having other forms of dysspermia. No normal sperm status was found in any of the patients (Table 4).

Among the 4 patients with recovery of spermatogenesis, 2 had cryptozoospermia; 1 patient had asthenozoospermia and 1 patient had oligozoospermia. The median time to recovery was 3.6 years (range, 1.5-6.7 years). All 4 patients had azoospermia in the first fertility assessment performed after treatment. The patients recovered 1.5, 2.5, 4.7, and 6.7 years after the end of therapy, respectively. Sperm analysis before treatment was available in 3 of 4 patients; 1 had azoospermia, 1 had OAT, and 1 had oligoasthenozoospermia. Improvement of the fertility status after treatment as compared with the status before treatment was observed in 2 patients. In 1 patient, the sperm count was 0.0×10^6 and 0.1×10^6 before and after treatment, respectively; in the second patient, sperm count was 19.7×10^6 and 32.4×10^6 before and after treatment, respectively. There was no significant difference in age between patients with azoospermia (median age, 26 years; range, 16-41 years) and those without (median age, 23 years; range, 22-37 years; $P > .999$, Wilcoxon rank-sum test).

Importantly, there was no statistically significant difference in fertility status between the group of patients treated with 8 cycles of BEACOPP baseline and those treated with 8 cycles of BEACOPP escalated; the infertility rate was 93% and 87%, respectively ($P > .999$; Fisher exact test). Regarding the influence of radiotherapy on fertility status, the infertility rate was 100% among patients treated with chemotherapy alone and 87.5% among the patients treated with combined modality. All 3 patients who received infradiaphragmal radiotherapy had azoospermia after treatment.

Table 4. Results of sperm analysis after treatment

Patient characteristics	Total, n = 38	BEACOPP baseline, n = 15	BEACOPP escalated, n = 23
Normozoospermia	0 (0)	0 (0)	0 (0)
Azoospermia	34 (89)	14 (93)	20 (87)
Other dyspermia	4 (11)	1 (7)	3 (13)

Data are number (%) of patients. $P > .999$, Fisher exact test.

With regard to the pretreatment and posttreatment sperm analysis available for 26 patients, the median sperm concentration before therapy was 21.2×10^6/mL (mean, 38.3×10^6/mL; range, 0.0-151.0 $\times 10^6$/mL). Normal sperm analysis was found in 6 (23%) of 26 patients. Azoospermia was observed in 2 (8%) patients and other dysspermia was observed in 18 (70%) patients. After treatment, the median sperm concentration was 0×10^6/mL (mean, 1.29×10^6/mL; range, 0.0-32.4 $\times 10^6$/mL); 23 (88%) patients had azoospermia and 3 (12%) patients had other forms of dysspermia. None of the patients had normozoospermia. The difference in sperm quality before and after treatment among the 26 patients was statistically significant ($P < .001$; signed-rank test).

Hormonal analysis

Availability of hormone serum levels prior to treatment was as follows: FSH, 18 patients; LH and testosterone, 17 patients. The median serum levels were FSH, 4.3 U/L (mean, 4.4 U/L; range, 1.9-7.0 U/L); LH, 3.2 U/L (mean, 4.1 U/L; range, 1.5-7.8 U/L); and testosterone, 5.3 μg/L (mean, 7.5 μg/L; range, 1.2-19.0 μg/L). Abnormal levels for FSH, LH, and testosterone (for the normal values, see Table 5) were found in 0%, 6%, and 41% of patients, respectively.

After treatment, serum levels were available from 15 patients for FSH, as well as from 14 patients for LH and for testosterone. The median levels were FSH, 17.4 U/L (mean, 16.9 U/L; range, 6.9-25.5 U/L); LH, 6.15 U/L (mean, 6.8 U/L; range, 1.8-24.9 U/L); and testosterone, 3.61 μg/L (mean, 4.3 μg/L; range, 2.3-10.8 μg/L). Most patients (93%) had abnormal FSH values after treatment. Regarding testosterone and LH levels, the number of patients with abnormal levels after treatment was less pronounced (57% and 21%, respectively). There was a significant difference between the pre- and posttreatment median level of FSH ($P = .008$; signed-rank test), but not for LH and testosterone ($P = .203$ and $P = .844$, respectively; signed-rank test). The results of available FSH, LH, and testosterone serum levels before and after treatment are presented in Table 5.

There was no significant difference in median FSH, LH, and testosterone serum levels between patients treated with BEACOPP baseline and those given BEACOPP escalated ($P > .999$; Wilcoxon rank-sum test). Moreover, we were unable to find a

Table 5. Results of hormone analysis before and after treatment

Hormone	Before treatment	After treatment	P*
FSH (normal values, 1.0-7.0 U/L)			
Total no. patients	18	15	—
Less than 1.0 U/L, no. (%)	0 (0)	0 (0)	—
1.0 to 7.0 U/L, no. (%)	18 (100)	1 (7)	—
More than 7.0 U/L, no. (%)	0 (0)	14 (93)	—
Median, U/L (range)	4.3 (1.9-7.0)	17.4 (6.9-25.5)	.008
LH (normal values, 2.0-10.0 U/L)			
Total no. patients	17	14	—
Less than 2.0 U/L, no. (%)	1 (6)	1 (7)	—
2.0 to 10.0 U/L, no. (%)	16 (94)	11 (79)	—
More than 10.0 U/L, no. (%)	0 (0)	2 (14)	—
Median, U/L (range)	3.2 (1.5-7.8)	6.15 (1.8-24.9)	.203
Testosterone (normal values, 3.5-8.6 μg/L)			
Total no. patients	17	14	—
Less than 3.5 μg/L, no. (%)	2 (12)	7 (50)	—
3.5 to 8.6 μg/L, no. (%)	10 (59)	6 (43)	—
More than 8.6 μg/L, no. (%)	5 (29)	1 (7)	—
Median, μg/L (range)	5.3 (1.2-19.0)	3.61 (2.3-10.8)	.844

— indicates not applicable.
*Signed-rank test.

statistically significant relationship between hormone levels (FSH, LH, and testosterone) after treatment and fertility status ($P > .999$; logistic regression).

Predictive factors

None of the tested predictive factors was statistically significant for azoospermia in univariate and multivariate analysis: age ($P = .871$), clinical stage ($P = .758$), elevated erythrocyte sedimentation rate ($P = .911$), B symptoms ($P = .568$), large mediastinal mass ($P = .651$), extranodal disease ($P = .969$), and 3 or more lymph nodes ($P = .961$).

Discussion

These are the most relevant findings from present study: (1) the majority of patients with advanced-stage HL become azoospermic after treatment with 8 cycles of BEACOPP; (2) there was no difference in the azoospermia rate between patients treated with 8 cycles of BEACOPP baseline and those given 8 cycles of BEACOPP escalated; (3) most patients with advanced HL stages have inadequate semen quality prior to treatment; (4) FSH levels were elevated in most patients after treatment but did not correlate with fertility status in the present analysis, which is most probably related to the low number of patients.

This is the most comprehensive analysis for HL to date in patients treated with BEACOPP, a new effective regimen particularly in advanced stages of disease. BEACOPP can induce high overall and long-lasting response rates in patients with advanced-stage HL.[2] As nearly all chemotherapeutic regimens induce a variety of side effects, it is important to assess different aspects of toxicity associated with BEACOPP. We recently reported the incidence of non-HL, secondary leukemias, solid tumors, and the impact of treatment on female fertility in patients with HL.[5,6,13,21] Since data on male fertility after BEACOPP were missing, the present study was eagerly awaited. We observed testicular dysfunction in most of our patients after treatment with BEACOPP, with 89% (34 of 38) being azoospermic. Of the remaining 4 patients, 2 had severe damages in spermatogenesis. Interestingly, there was no difference in testicular function between patients receiving 8 cycles of BEACOPP baseline compared with those treated with 8 cycles of BEACOPP escalated (93% vs 87%, respectively; $P > .999$). As these 2 regimens differ in the dose of cyclophosphamide (650 mg/m^2 vs 1250 mg/m^2), doxorubicin (25 mg/m^2 vs 35 mg/m^2), and etoposide (100 mg/m^2 vs 200 mg/m^2), these data suggest that higher doses of these drugs do not have an additional negative effect on male fertility, although the number of patients is low. Furthermore, the fertility rates reported in this study do not differ significantly from those reported after regimens such as MOPP/ABVD (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine; 87%), COPP/ABVD (86%), and ChIVPP/EVA (chlorambucil, vinblastine, prednisolone, procarbazine, doxorubicin, vincristine, etoposide; 95%).[22-24] Our data from 10 patients with advanced HL treated with 8 cycles of COPP/ABVD show 90% of patients with azoospermia after treatment. Similar rates of azoospermia after treatment were also reported with older regimens such as MVPP (mechlorethamine, vinblastine, procarbazine, and prednisone; 88%; 36 of 41 patients), MOPP (86%; 25 of 29 patients), and COPP (100%; 19 of 19 patients).[16,25,26] There are some indications that fertility is more often preserved with MOPP/ABVD compared with MOPP.[27] The cumulative dose of the cytostatic drugs given seems to be one of the key determinants. The study of da Cunha et al assessing MOPP-induced gonadotoxicity showed that azoospermia was significantly higher after more than 3 cycles of MOPP compared with gonadotoxicity observed after less than 3 cycles of treatment (91% vs 14%, respectively).[28] Another factor reported to affect fertility in patients with HL is the inclusion of alkylating agents in the treatment regimens.[17,26] After therapy with ABVD, one of the most often used regimens in the treatment of HL, azoospermia was observed in 0% to 4% of patients.[17,26]

In addition, infradiaphragmal radiation has been reported to affect male fertility.[28] Da Cuhna et al documented more infertility among patients with HL after treatment with MOPP who had pelvic radiotherapy compared with those who did not receive pelvic radiotherapy.[28] Further, Dubaey et al described the differences in fertility between patients having different infradiaphragmal radiation fields.[29] In the present study, all 3 patients who received

infradiaphragmal radiotherapy had persistent azoospermia despite not having received radiotherapy to the testis. However, due to the very small number of cases we were unable to make valid conclusion.

Most patients in our study had inadequate semen quality before treatment, with 8% having azoospermia and 70% having other forms of dysspermia. Normozoospermia was observed only in 23% of patients. Similar results were reported in other studies.[12,14,18,26] The underlying mechanism of infertility in patients with HL before treatment is still unknown. Suspected factors include damage in the germinal epithelium, disturbances in the hypothalamic-hypophysial axis, and the impact of the disease-related cytokines on spermatogenesis.[18,30-32] We could confirm that in our series the semen characteristics before treatment do not seem to be predictive for the recovery of testicular function, as reported by others.[14,24] Interestingly, we also observed improvement of sperm quality after treatment in 2 patients.

Serum levels of FSH, LH, and testosterone before treatment were normal in most patients and did not correlate with sperm quality as shown in previous studies.[18,33] The FSH levels after treatment were elevated in most patients (93%), while increased levels of testosterone and LH after treatment were observed in fewer patients (57% and 21%, respectively). The median posttreatment FSH level was significantly higher compared with the median pretreatment value. No significant difference was observed in the median LH and testosterone values tested before and after treatment. Similar results have been reported elsewhere[17,22,24] and confirm the hypothesis that spermatogonia are sensitive to chemotherapy, whereas Sertoli and Leyding cells are more resistant.[16,34] Since increased FSH serum levels have been associated with germinal epithelial damage, our findings support the hypothesis that male infertility after treatment is at least in part due to germinal epithelial damage.[22,26] Although FSH levels were elevated after treatment, there was no statistically significant correlation between FSH levels and fertility status, probably due to the small number of patients in our cohort. Similar findings have been reported by Viviani et al.[24] Using a larger group of patients with HL treated with different regimens, we observed a significant correlation between FSH levels and fertility status.[35] A significant association between FSH levels and male fertility status has also been observed by others.[16] Thus, FSH levels after treatment may be of predictive significance for fertility in patients with HL.

We were not able to detect significant risk factors for azoospermia after treatment, which was at least in part related to the small number of evaluated patients. Rovo et al assessed spermatogenesis in long-term survivors after allogenic stem cell transplantation using multivariate Cox regression analysis and reported that age older than 25 years at the time of transplantation and conditioning regimen using total body irradiation (TBI) were significantly associated with low probability for spermatogenesis.[36]

The question is whether incomplete sperm production such as oligozoospermia or other forms of dysspermia are of clinical relevance. This might indeed be the case, as patients with severe oligozoospermia have been reported to father healthy children.[37] Moreover, reduced fertility after chemotherapy can be compensated for by improved assisted reproduction techniques.[38] Another very important aspect in the judgement of fertility of male patients after curative chemotherapy is the fact that even patients who were azoospermic for more than 4 years can still recover as observed in 2 patients in our series and by others.[36] Nevertheless, fertility status can be assessed by analyzing FSH and possibly inhibin B[39] serum levels. It is advisable that such analyses should also be performed as means of fertility screening in future HL trials.

In conclusion, we demonstrated that 8 cycles of BEACOPP induce sterility in most male patients with advanced-stage HL. Since recovery was observed in selected patients, longer follow-up and monitoring of FSH levels is required in these patients.

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Authorship

Contribution: M.S., A.J., and A.E. designed the research. M.S. and T.R. analyzed data. M.S. wrote the paper. L.N. and B.P. were responsible for data collection. A.J. and A.E. designed the research and reviewed the paper. V.D. is chairman of the GHSG.

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A complete list of the members of the GHSG is provided in Document S1, available on the *Blood* website.

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References

1. Rosenberg SA. The management of Hodgkin's disease: half a century of change: the Kaplan Memorial Lecture. Ann Oncol. 1996;7:555-560.
2. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med. 2003; 348:2386-2395.
3. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol. 2004;22:2835-2841.
4. Greco RS, Acheson RM, Foote FM. Hodgkin disease in Connecticut from 1935 to 1962: the bimodal incidence curve in the general population and survival in untreated patients. Arch Intern Med. 1974;134:1039-1042.
5. Rueffer U, Josting A, Franklin J, et al. Non-Hodgkin's lymphoma after primary Hodgkin's disease in the German Hodgkin's Lymphoma Study Group: incidence, treatment, and prognosis. J Clin Oncol. 2001;19:2026-2032.
6. Josting A, Wiedenmann S, Franklin J, et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2003;21:3440-3446.
7. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol. 2000;18:498-509.
8. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94:182-192.
9. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003;95: 971-980.
10. Hirsch A, Vander Els N, Straus DJ, et al. Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease. J Clin Oncol. 1996;14:1297-1305.
11. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. JAMA. 2003;290:2831-2837.
12. Chapman RM, Sutcliffe SB, Malpas JS. Male gonadal dysfunction in Hodgkin's disease: a prospective study. JAMA. 1981;245:1323-1328.

13. Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2005;23:7555-7564.
14. Redman JR, Bajorunas DR, Goldstein MC, et al. Semen cryopreservation and artificial insemination for Hodgkin's disease. J Clin Oncol. 1987;5: 233-238.
15. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. J Clin Oncol. 2002;20:1880-1889.
16. Kreuser ED, Xiros N, Hetzel WD, Heimpel H. Reproductive and endocrine gonadal capacity in patients treated with COPP chemotherapy for Hodgkin's disease. J Cancer Res Clin Oncol. 1987;113:260-266.
17. Kulkarni SS, Sastry PS, Saikia TK, Parikh PM, Gopal R, Advani SH. Gonadal function following ABVD therapy for Hodgkin's disease. Am J Clin Oncol. 1997;20:354-357.
18. Rueffer U, Breuer K, Josting A, et al. Male gonadal dysfunction in patients with Hodgkin's disease prior to treatment. Ann Oncol. 2001;12: 1307-1311.
19. World Health Organization. Sperm-Cervical Mukus Interaction. 3rd ed. New York: Cambridge University Press. 1993:1-67.
20. Eliasson R, Hellinga F, Lubcke F. Empehlungen zur Nomenklatur in der Andrologie [Recommendation for nomenclature in andrology]. Andrologie. 1970;2:1257.
21. Behringer K, Josting A, Schiller P, et al. Solid tumors in patients treated for Hodgkin's disease: a report from the German Hodgkin Lymphoma Study Group. Ann Oncol. 2004;15:1079-1085.
22. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Gonadal function following chemotherapy for Hodgkin's disease: a comparative study of MVPP and a seven-drug hybrid regimen. J Clin Oncol. 1995;13:134-139.
23. Kreuser ED, Felsenberg D, Behles C, et al. Long-term gonadal dysfunction and its impact on bone mineralization in patients following COPP/ABVD chemotherapy for Hodgkin's disease. Ann Oncol. 1992;3:105-110.
24. Viviani S, Ragni G, Santoro A, et al. Testicular dysfunction in Hodgkin's disease before and after treatment. Eur J Cancer. 1991;27:1389-1392.
25. Waxman JH, Terry YA, Wrigley PF, et al. Gonadal function in Hodgkin's disease: long-term follow-up of chemotherapy. Br Med J (Clin Res Ed). 1982; 285:1612-1613.
26. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease: comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol. 1985;21:601-605.
27. Longo DL, Glatstein E, Duffey PL, et al. Alternating MOPP and ABVD chemotherapy plus mantlefield radiation therapy in patients with massive mediastinal Hodgkin's disease. J Clin Oncol. 1997;15:3338-3346.
28. da Cunha MF, Meistrich ML, Fuller LM, et al. Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. J Clin Oncol. 1984;2:571-577.
29. Dubey P, Wilson G, Mathur KK, et al. Recovery of sperm production following radiation therapy for Hodgkin's disease after induction chemotherapy with mitoxantrone, vincristine, vinblastine, and prednisone (NOVP). Int J Radiat Oncol Biol Phys. 2000;46:609-617.
30. Huleihel M, Lunenfeld E, Levy A, Potashnik G, Glezerman M. Distinct expression levels of cytokines and soluble cytokine receptors in seminal plasma of fertile and infertile men. Fertil Steril. 1996;66:135-139.
31. Dousset B, Hussenet F, Daudin M, Bujan L, Foliguet B, Nabet P. Seminal cytokine concentrations (IL-1beta, IL-2, IL-6, sR IL-2, sR IL-6), semen parameters and blood hormonal status in male infertility. Hum Reprod. 1997;12:1476-1479.
32. Schulte HM, Bamberger CM, Elsen H, Herrmann G, Bamberger AM, Barth J. Systemic interleukin-1 alpha and interleukin-2 secretion in response to acute stress and to corticotropin-releasing hormone in humans. Eur J Clin Invest. 1994;24:773-777.
33. Ragni G, Bestetti O, Santoro A, Viviani S, Di Pietro R, De Lauretis L. Evaluation of semen and pituitary gonadotropin function in men with untreated Hodgkin's disease. Fertil Steril. 1985;43: 927-930.
34. Bramswig JH, Heimes U, Heiermann E, Schlegel W, Nieschlag E, Schellong G. The effects of different cumulative doses of chemotherapy on testicular function: results in 75 patients treated for Hodgkin's disease during childhood or adolescence. Cancer. 1990;65:1298-1302.
35. Sieniawski M, Reineke T, Josting A, Diehl V, Engert A. Fertility in male Hodgkin lymphoma patients: a report of German Hodgkin Study Group [abstract]. Blood. 2006;101: abstract no. 101.
36. Rovo A, Tichelli A, Passweg JR, et al. Spermatogenesis in long-term survivors after allogeneic hematopoietic stem cell transplantation is associated with age, time interval since transplantation, and apparently absence of chronic GVHD. Blood. 2006;108:1100-1105.
37. Petti N, Anghel G, Schimberni M, et al. Successful paternity with microassisted fertilization after total body irradiation-based conditioning for autologous bone marrow transplantation. Hematol J. 2003;4:285-288.
38. Chan PT, Palermo GD, Veeck LL, Rosenwaks Z, Schlegel PN. Testicular sperm extraction combined with intracytoplasmic sperm injection in the treatment of men with persistent azoospermia postchemotherapy. Cancer. 2001;92:1632-1637.
39. Andersson AM, Petersen JH, Jorgensen N, Jensen TK, Skakkebaek NE. Serum inhibin B and follicle-stimulating hormone levels as tools in the evaluation of infertile men: significance of adequate reference values from proven fertile men. J Clin Endocrinol Metab. 2004;89:2873-2879.