

Original Research Article

Risk factors for impaired gonadal function in female Hodgkin lymphoma survivors: final analysis of a retrospective multicenter joint study from Italian and Brazilian Institutions

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Abstract

Hodgkin lymphoma (HL) is one of the most common types of cancer in the young and one of the most curable forms of cancer. Therefore, there has been an increasing interest in the study of long-term morbidities. The aims of the present study were to evaluate the prevalence and risk factors for impaired gonadal function in a retrospective cohort of 238 HL female survivors from Italy and Brazil and to analyse the role of oral contraceptives (OC) and GnRH-analogues. Besides data collection from HL databases, a specific questionnaire was administered to collect data on gonadal function. The median age at diagnosis was 25 years and the median follow-up was 7 years. Overall, 25% of the patients developed impaired gonadal function. Older age at diagnosis, front-line therapies containing alkylating agents and more than one treatment were independent risk factors, whereas the use of OC or GnRH-a reduced independently the risk of impaired gonadal function. The fertility rate among fertile survivors was low when compared with the general population. We confirmed that older age, type of front-line chemotherapy and a higher number of therapies are associated with gonadal function impairment in terms of infertility and premature menopause in female HL survivors. Also, the use of GnRH-a or OC was independently identified as a protective factor. Further prospective studies are needed to better understand the barriers to parenthood in HL survivors. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Hodgkin lymphoma; survivors; fertility; GnRH-a

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Introduction

Hodgkin lymphoma (HL) is one of the most common types of cancer among the young and one of the most curable forms of cancer, with a 5-year relative survival of 87% in the last decade [1]. Currently, there are over 300 000 survivors of HL in North America and Europe [2]. For these reasons, there has been a growing interest in the study of long-term morbidities of HL treatment.

Infertility and premature menopause are the major concerns for long-term survivors [3]. Different rates of

secondary amenorrhea and premature menopause have been reported, and they vary according to the patients' age, stage of disease, dose and intensity of chemotherapy and use of radiation therapy. The two most frequently used chemotherapy regimens for the treatment of advanced HL differ substantially on this regard. Whereas 51% of female HL survivors who received eight cycles of escalated BEACOPP had permanent amenorrhea, ABVD appears to have little if any impact on female fertility [4–8].

A few studies evaluating the role of oral contraceptives (OC) and gonadotropin-releasing hormone analogues

(GnRH-a) during HL treatment to prevent secondary ovarian failure have been published [9–11]. One of the hypotheses is that these drugs might prevent the increase in follicle stimulating hormone concentration, thus avoiding accelerated follicular atresia [12]. However, the data are controversial and come mostly from retrospective studies and small series [9,10]. The only randomized prospective trial aiming to compare OC and GnRH-a was closed prematurely, because neither arm protected ovarian function [13].

In 2009, the *Gruppo Italiano Studio Linfomi* (GISL) launched an observational retrospective study to evaluate gonadal toxicity related to treatment for HL. GISL has been collecting data on patients with HL for over 20 years, and this database contains a homogeneous series of consecutive patients with HL. Furthermore, a consecutive series of patients from Brazil was added for the present study.

The aims of the present study were to evaluate the frequency of gonadal toxicity in a large series of HL female survivors, identify risk factors associated with gonadal damage and evaluate the role of OC or GnRH-a during HL treatment for the preservation of fertility and for preventing premature menopause.

Patients and methods

A retrospective analysis was conducted in female HL survivors registered in databases in Italy and Brazil. A complete data set for the study was retrieved from the archives of GISL and from the archives of three university hospitals in Brazil (Federal University of Rio de Janeiro, University of Campinas and Santa Casa de São Paulo). The GISL Trial Office in Modena coordinated the data collection, assessed the coherence of data and monitored the study. This study fully complied with all provisions of the Declaration of Helsinki and was approved by the Ethics Committee of each participating institution. All patients signed an informed consent.

Patients included in the study were aged 14–40 years at diagnosis, with biopsy-proven Hodgkin lymphoma, diagnosed from January 1985 to July 2009 and alive in February 2011. Patients with progressive or recurrent disease at the time of the study were not included. A minimum follow-up of 18 months was required. Patients must have had regular menstrual cycles before treatment, no previous or concomitant gynecological diseases affecting reproductive function and no chemo-radiotherapy for other neoplasms.

A specific questionnaire was administered in order to collect data on gonadal function, including the pretreatment information. The questionnaire also contained questions about the number of pregnancies before treatment and the use OC and GnRH-a during treatment. Also, patients were asked about the recovery of regular menses after treatment or the development of irreversible amenorrhea after treatment, the attempt to conceive children after the treatment, whether they succeed or not, and the number of pregnancies after treatment.

Baseline clinical characteristics at diagnosis recorded were age, Ann Arbor stage (I-IIA or IIB-IV), presence

of B symptoms, front-line treatment, radiation therapy, response after front-line treatment, salvage chemotherapy regimens and treatment with peripheral blood stem cell transplantation. Regarding front-line treatment, patients were categorized in three groups: the first group consisted of patients treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or VBM (vinblastine, bleomycin and methotrexate), the second group included standard BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) and COPPEBVCAD (cyclophosphamide, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine), and the third group consisted of patients treated with escalated BEACOPP. Because no specific recommendations were available, the decision to use OC or GnRH-a was left to each physician's discretion.

Endpoint definitions

The primary endpoint was impaired gonadal function. Patients were considered to have impaired gonadal function if irreversible amenorrhea developed after treatment or if they failed to conceive despite pursuing pregnancy with regular menses. Patients were considered to have preserved gonadal function if they became pregnant after treatment or if they had regular menses but decided not to attempt to conceive. Irreversible amenorrhea was defined as absence of resumption of normal menstrual cycles in the 6 months subsequent to the conclusion of treatment. Impaired gonadal function was further assessed considering the rate of premature menopause that was defined as the presence of early permanent amenorrhea after treatment.

An additional endpoint was the fertility rate (number of pregnancies/total number of patients) before and after treatment, which was calculated among patients with preserved gonadal function.

Statistical analysis

Standard descriptive analyses were carried out. For a crude association analysis, categorical data were analysed using the chi-square or Fisher's exact test (two-sided). Univariate and multivariate logistic regression analyses were conducted to identify factors associated with impaired gonadal function. Variables yielding p -values <0.2 in the univariate analysis were included in a backward multivariate logistic regression analysis. Odds ratios with 95% confidence intervals were computed. Two-tailed p -values <0.05 were considered statistically significant. The SPSS version 17.0 software (Chicago, IL, USA) was used for data analysis.

Results

Among 242 patients initially identified in the databases, four were excluded because they had previous gynecological diseases affecting the reproductive function. The remaining

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238 fulfilled eligibility criteria for the present study (160 patients from Italy and 78 from Brazil).

The median age of the patients at the time of diagnosis was 25 (14–40 years). The median follow-up was 7 (1.5–25 years). The main characteristics at the time of diagnosis are shown in Table 1.

A flowchart describing the distribution of patients in the different categories of gonadal function status

Table 1. Baseline characteristics

Characteristics	N (%)
Age (years)	
≤30	175 (74)
>30	63 (26)
Stage	
I–IIA	103 (43)
IIB–IV	135 (57)
Front-line treatment	
ABVD and VBM	174 (73)
COPPEBVCAD/standard BEACOPP*	49 (21)
Escalated BEACOPP*	14 (6)
Radiation therapy	
Yes	146 (62)
No	90 (38)
Response after first treatment	
Complete remission	226 (95)
Partial remission	5 (2)
No response	7 (3)
PBSCT	
Yes	20 (8)
No	218 (92)

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or VBM (vinblastine, bleomycin and methotrexate), COPPEBVCAD denotes cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin and BEACOPP denotes bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. PBSCT denotes peripheral blood stem cell transplantation.

*The median number of cycles of COPPEBVCAD/standard BEACOPP was 6 (range 2–8) and of escalated BEACOPP was 6 (range 4–8).

is shown in Figure 1. Overall, 25% of the patients were considered to have impaired gonadal function. No difference in the rates of impaired gonadal function was observed between patients from Italy and Brazil (23% and 28%, $p = 0.43$) respectively.

Factors associated with impaired gonadal function

The comparison of baseline characteristics between patients with normal and impaired gonadal function is shown in Table 2. In the univariate analysis, older age (>30 years), advanced-stage, front-line treatment with alkylating agents, number of treatments received and no use of radiation therapy were associated with an increased risk of impaired gonadal function. On the other hand, the use of OC or GnRH-a during treatment was associated with lower rates of impaired gonadal function. These parameters were included in the multivariate logistic regression, and the factors that remained independently associated with impaired gonadal function were age at diagnosis >30 years, front-line treatment with alkylating, number of treatments received and no use of OC or GnRH-analogues during treatment (Table 3). Regarding premature menopause, the same risk and protective factors were found in univariate and multivariate analysis (data not shown).

Pregnancies before and after treatment in patients with normal gonadal function

A total of 50 (28%) women had already been pregnant before treatment, and among them, 19 had two or more pregnancies. The fertility rate before treatment was 0.42, 0.39 in Italy and 0.5 in Brazil, ($p = 0.49$)

After treatment, 58 (32%) women become pregnant, and among them, 11 had two or more children. The

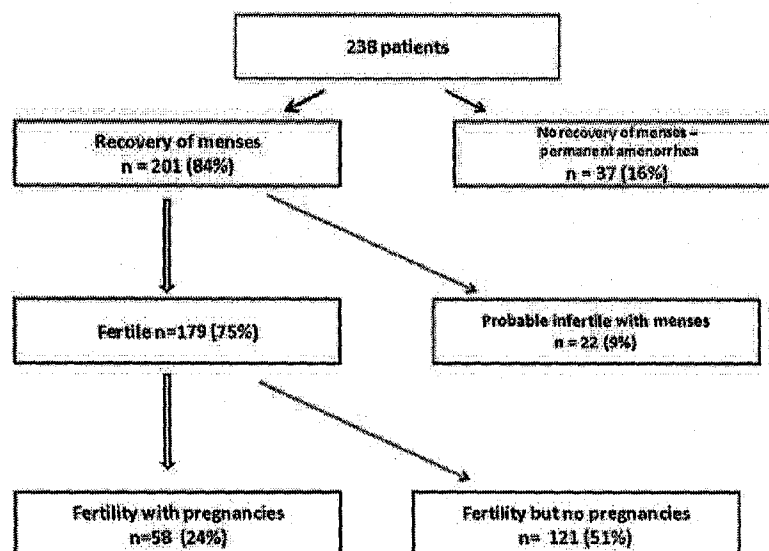


Figure 1. Flow chart illustrating the distribution of patients according to the status of gonadal function

Table 2. Comparison of the baseline characteristics between patients with normal and impaired gonadal function

	Normal gonadal function	Impaired gonadal function	p-value
Age (years)			
≤30	140 (80)	35 (20)	0.006
>30	39 (62)	24 (38)	
Stage			
I-IIA	86 (84)	17 (16)	0.01
IIB-IV	93 (69)	42 (31)	
Front-line therapy			
ABVD or VBM *	138 (79)	36 (21)	0.037
COPPEBVCAD/standard BEACOPP	32 (65)	17 (35)	
Escalated BEACOPP	8 (57)	6 (43)	
Infertility prophylaxis			
None	35 (55)	29 (45)	< 0.001
Oral contraceptive	59 (81)	14 (19)	
GnRH-a	85 (84)	16 (16)	
Radiation therapy			
No	58 (64)	32 (36)	0.003
Yes	120 (82)	26 (18)	
Number of therapies			
I	172 (81)	41 (19)	<0.001
>I	7 (28)	18 (72)	
Number of pregnancies before treatment			
0	129 (78)	37 (22)	0.19
≥ 1	50 (69)	22 (31)	

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or VBM (vinblastine, bleomycin and methotrexate), COPPEBVCAD denotes cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin and BEACOPP denotes bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, GnRH-a denotes gonadotropin-releasing hormone analogues, PBSCT denotes peripheral blood stem cell transplantation.

*No difference was found between the rate of impaired gonadal function in patients who received four or less cycles and for those who received more than four cycles was 25% ($p = 0.19$).

Table 3. Univariate and multivariate analysis of factors associated with impaired gonadal function

	Univariate regression analysis			Multivariate regression analysis		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Age (years)						
≤30	1			1		
>30	2.4	1.3–4.6	0.005	2.99	1.39–6.41	0.005
Stage						
I-IIA	1					
IIB-IV	2.28	1.2–4.3	0.011			
Front-line therapy						
ABVD and VBM	1			1		
COPPEBVCAD/st BEACOPP	2	1.02–4	0.015	2.44	1.06–5.66	0.03
Escalated BEACOPP	2.87	0.94–8.8	0.06	4.24	1.12–16	0.03
Prevention						
No	1			1		
Oral contraceptive	0.29	0.13–0.61	0.001	0.22	0.09–0.54	0.005
Analogues GNRH	0.23	0.11–0.47	<0.001	0.14	0.06–0.35	<0.001
Radiation therapy						
No	1					
Yes	0.39	0.21–0.72	0.002			
Number of therapies						
I	1			1		
>I	10.8	4.22–27.5	<0.001	19	6.48–58.6	<0.001
Number of pregnancies before HL						
0	1					
≥1	1.5	0.82–2.85	0.18			

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or VBM (vinblastine, bleomycin and methotrexate), COPPEBVCAD denotes cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin and BEACOPP denotes bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone. GNRH denotes gonadotropin-releasing hormone analogues. PBSCT denotes peripheral blood stem cell transplantation.

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post-treatment fertility rate was 0.40, 0.39 in Italy and 0.41 in Brazil ($p=0.46$).

The overall fertility rate (before and after treatment) was 0.82, 0.78 in Italy and 0.91 in Brazil. ($p=0.26$)

Discussion

Long-term complications of therapy for HL have become a major concern. Infertility is one of the most feared consequences for survivors in reproductive age. In the present study, we sought to investigate the frequency of gonadal damage in a series of 238 female HL survivors with a median follow-up of 7 years and also to identify factors associated with impairment of gonadal function.

Overall, the frequency rate of impaired gonadal function was 25%. The endpoint definition of impaired gonadal function used was based on clinical evidence, as in previous studies [4,5,14]. Because the presence of normal menstrual activity is not the best surrogate for normal ovarian function, this information was combined with the answers of a questionnaire, in order to establish whether the patient had attempted to conceive and if she had succeeded. Patients with regular menses who did not succeed in conceiving were considered to have impaired gonadal function. A similar analysis using the more objective and stricter definition of impaired gonadal function as patients with irreversible amenorrhea was also performed, and the results regarding risk and protective factors were exactly the same.

Older age at diagnosis, front-line therapies containing alkylating agents and more than one treatment were identified as independent risk factors for infertility and premature menopause, in agreement with previous studies [4,5]. As shown in Tables 2 and 3, a gradient in the rate of gonadal impairment function was observed according to the type of front-line therapy, with standard BEACOPP and escalated BEACOPP resulting respectively in two and nearly three times more risk of infertility. This observation has immediate implications for patient care, because most HL patients are diagnosed in their reproductive years, and many young, still childless female patients are affected. Unfortunately, no standard effective cryopreservation approach is available for women. Thus, the fertility risks imposed by more intensive chemotherapy regimens must be individually discussed, especially with women over 30 years old. In this regard, it should be pointed out that even in patients treated with ABVD, approximately 20% had impaired gonadal function in the present study. This result can be considered higher than expected. This impairment could be due to the cumulative effect of salvage therapies for relapsed patients and also by wider definition of impaired gonadal function used in this study. Of note, in univariate analysis, radiation therapy was associated with a decreased risk of impaired gonadal function. This should be taken cautiously because it likely reflects the higher proportion use of radiation therapy among patients with localized disease (80/107, 75%) compared with advanced stage (74/147, 50%) ($p < 0.001$). Actually, the use of radiation therapy did not remain as an

independent risk factor for impaired gonadal function in multivariate analysis.

The role of GnRH-a or OC in preserving fertility and preventing premature menopause in female lymphoma patients receiving chemotherapy remains controversial [9,10,15–19]. In the present study, the use of OC or GnRH-a during treatment independently reduced the risk of impaired gonadal function and the occurrence of premature menopause. This is the first study with more than 200 HL patients with a long median follow-up to include a substantial number of patients using OC or GNRH and being treated with different chemotherapy regimens. These findings confirm our previous analysis in a different patient population [10]. Also, in another prospective non-randomized study, 97% of patients who received GnRH-a during HL treatment resumed ovulation and regular menses, compared with only 63% in a control group [9]. Furthermore, the randomized trial PROMISE-GIM6 showed that the use of GnRH-a in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause [20]. Recently, an analysis of fertility and gonadal function in female survivors after treatment of early-unfavourable HL within GHSG HD14 trial revealed that the prophylactic use of GNRH was independently associated to preservation of fertility [19]. On the other hand, the GHSG recently published the results of a randomized phase II trial comparing OC with GnRH-a in young female HL patients treated with escalated BEACOPP [13]. The trial was closed prematurely, after an interim analysis showed no evidence of protection of the ovarian reserve with either treatment. Taken together, the results of these studies suggest that the strategies to preserve fertility and normal gonadal function should be treatment adapted, so the prophylactic use of GnRH-a might be effective in young female patients with HL who receive ABVD or a short-course of BEACOPP. For those who receive full courses of BEACOPP, other strategies such as ovarian cryopreservation must be evaluated to preserve fertility.

An additional finding in the present study was that the overall fertility rate of fertile survivors of HL was lower than in the general population. The overall fertility rate gives a figure of the average number of children that would be born per woman if all women lived to the end of their childbearing years. In 2011, for the general population, this rate was 1.39 in Italy and 2.18 in Brazil [21]. In the present study, overall fertility rates among those considered fertile were 0.78 in Italy and 0.91 in Brazil. The rates after treatment were remarkably similar in Italy and Brazil (0.39 and 0.41), despite the different rates in the general population, suggesting that other barriers to parenthood, besides infertility might be operative after successful cancer treatment [22–24]. These barriers might include concerns about the possibility of disease relapse, psychological issues related with survivorship after cancer, difficulties in formulating plans for the future and financial concerns. A similar phenomenon has been observed in male cancer survivors who, quite unexpectedly, seldom use their deep frozen sperm cells. The rate of cryopreserved semen utilization in different studies has ranged from 3.7% to 16.3% [25–28]

In summary, we confirmed that older age at diagnosis, the type of front-line chemotherapy and a higher number of

therapies are associated with gonadal function impairment in female HL survivors. Also, the results of the present study and other recent reports suggest that the strategies to preserve fertility and gonadal function should be treatment adapted. Currently, ovarian reserve tests, such as follicle stimulating hormone, inhibin B, anti-Mullerian hormone and estradiol, and also ultrasound measurements are correlated with reproductive function in cancer survivors and may be more sensitive than menstrual activity in identifying an impaired ovarian reserve [29]. Further studies on developing ovarian reserve tests that might be able to more precisely assess ovarian function and predict reproductive success are needed and should be included in prospective trials addressing this issue. Finally, further prospective surveys to better understand the obstacles to parenthood in HL survivors must be incorporated in future trials.

Authors Contribution

Conception and design: S. Falorio, I. Biasoli, S. Luminari, F. Angrilli, M. Federico.

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Final approval of manuscript: S. Falorio, I. Biasoli, S. Luminari, G. Quintana, M. Musso, M. Dell'Olio, MR. Specchia, N. di Renzo, M. Cesaretti, G. Buda, D. Vallisa, D. Mannina, A. Andriani, CS. Chiattonne, MT Delamain, CA de Souza, N. Spector, F. Angrilli, M. Federico.

Conflict of Interest

The authors have declared no conflicts of interest.

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