Gonadal Function Recovery and Fertility in Women Treated with Chemo- and/or Radiotherapy for Hodgkin's and Non-Hodgkin Lymphoma

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Keywords

Lymphoma · Fertility · GnRH analogues · Chemotherapy

Abstract

Background: Fertility and gonadal function represent one of the most important aspects for long-term lymphoma survivors. **Aims:** The aim of our study was to determine possible risk factors, such as age at treatment, chemotherapeutic regimen, protection with oral contraceptives (OCs), and gonadotropin-releasing hormone (GnRH) analogues in female patients treated for Hodgkin's lymphoma (HL) or non-Hodgkin lymphoma (NHL) at a reproductive age. **Methods:** Patients between the age of 16 and 50 years at the time of HL or NHL diagnosis were selected. Eligible patients were requested to respond to a questionnaire by phone interview about fertility, menstrual status, sexual aspects, and treatment with OCs or GnRH analogues during chemotherapy. **Results:** The resumption of menstrual activity was associated with the use of the OCs and GnRH analogues during chemotherapy ($p = 0.008$ and 0.034 , respectively). At univariate analysis, the use

of OCs during chemotherapy was associated with a lower risk of amenorrhea (prevalence ratio [PR] = 0.37; 95% CI 0.17–0.82). A higher age at the time of treatment correlated positively with therapy-induced amenorrhea, with a difference of 12.8 years between the mean age at diagnosis of the women with therapy-induced amenorrhea and those who resumed their menses. Amenorrhea was significantly higher in women receiving R-CHOP than in women treated with ABVD (PR = 6.00; 95% CI 2.32–15.54). Moreover, NHL had an infertility PR of 1.51 (95% CI 0.86–2.45) at multivariate analysis compared to HL. **Conclusions:** This study suggests a possible role of pharmacological prophylaxis with OCs and GnRH analogues.

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Introduction

Significant improvement in the survival rates of patients with aggressive lymphoma has been achieved in the last decades.

According to the US National Cancer Institute (NCI), the 5-year survival is 86.2% for Hodgkin's lymphoma (HL) and 70.7% for non-Hodgkin lymphoma (NHL) [1], and consequently, the focus shifted on long-term toxicities. Given the relatively high incidence of lymphomas in women of childbearing age and the rising trend of delaying pregnancy until later in life, the issue of fertility preservation became increasingly important.

Therefore, discussing treatment-related fertility risks and fertility preservation options with patients is mandatory, as the lack of information is the main impediment to fertility preservation. A recent study showed that 95% of the HL and 94% of the NHL patients were informed about the treatment-related infertility risk [2], but there are heterogeneous data from different cancer care settings. Referring young patients to a fertility specialist consultation was associated with significantly greater satisfaction and was helpful with decision-making [3].

Clinicians demonstrated an increasing interest in using a pharmacological prophylaxis with oral contraceptives (OCs) or gonadotropin-releasing hormone (GnRH) analogues in the last years, but the real effectiveness is still controversial.

A Cochrane review demonstrated GnRH agonists as effective to resume menses and ovulation after chemotherapy and reducing the risk of amenorrhea [4], but a recent multicentric study revealed that the use of GnRH analogues was not useful to reduce chemotherapy-induced premature ovarian failure (POF) in young patients with lymphoma [5].

There is little evidence regarding the role of OCs in preserving fertility, and only few studies showed lower POF rates in OCs-treated patients [6]. A retrospective study reported that amenorrhea was more common in women not taking OCs compared with women on OCs during chemotherapy (44.1 vs. 10.1%, respectively; $p < 0.0001$) [7].

It should also be taken into account that patients with lymphoma have a diminished ovarian reserve when compared with healthy controls and patients with other malignancies [8].

In addition to infertility, another important late effect that should be considered is the occurrence of premature menopause and the related long-term health consequences.

The aim of our study was to determine possible risk factors, such as age at treatment, chemotherapeutic regimen, and protection with OCs and GnRH analogues in female patients treated for HD or NHL at a reproductive age.

Patients and Methods

Patient Selection

Patients between the age of 16 and 50 years at the time of HL or NHL diagnosis were selected. Patients who were already in menopause at the time of diagnosis were excluded. All patients were treated between 1995 and 2012, and all of them were in ongoing remission since at least 5 years after therapy. Eligible patients were requested to respond to a questionnaire by phone interview.

Questionnaire

Menstrual status, treatment with OCs or GnRH analogues during chemotherapy, pregnancies, and offspring after therapy were evaluated. Additional questions referred to the methods of fertility preservation before therapy. For women who were already in menopause at the time of the interview, we investigated some of the menopausal symptoms such as hot flashes, osteoporosis, decreased libido, mood swings, and age of the onset of menopause.

Statistics

Demographics and disease characteristics were summarized using descriptive statistics. The mean, standard deviation, minimum, median, and maximum were calculated for numerical parameters. Summary statistics were expressed as numbers (percentages) or means + standard deviation (SD), as appropriate. Independent t tests or Wilcoxon rank-sum tests for continuous variables and Pearson's χ^2 tests or Fisher's exact tests for categorical variables were used. Associations of treatment-induced amenorrhea with multiple risk factors (age at diagnosis, chemotherapy regimen, relapsed disease, radiotherapy, and the use of OCs before and during chemotherapy) were characterized by prevalence ratios (PR) and associated 95% confidence intervals (95% CI), estimated by fitting Poisson regression models with robust estimates of variance [9]. Univariate analyses for each factor were calculated for each trial, and then p values for the comparison of all clinical trials were performed. The level of significance was set at $p < 0.05$ (two-sided). Statistical analyses were performed with STATA 14.2 SE (Stata Corp., College Station, TX, USA).

Results

Patients' Characteristics

A total of 97 patients answered the questionnaire. The median observation time after treatment was 12 years (range 5–23). Sixty-one patients were affected by HL, 35 patients had a NHL, and 1 patient had a composite HL and NHL.

The median age at the time of treatment was 28 years (range 16–48) in the HL group and 37 years (range 18–49) in the NHL group. Overall, the median age at diagnosis was 31 years (range 16–49). There were 66% with I/II stage and 34% with III/IV stage.

Combined-modality (chemotherapy + radiotherapy) treatment was the most commonly used first-line therapy (59%), while 41% were treated only with chemotherapy.

Only 5% of all patients received subdiaphragmatic irradiation.

All HL patients were treated with ABVD or ABVD-like regimens, whereas the NHL patients were treated with R-CHOP, VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), and other regimens. Seventeen patients (17%) relapsed after first-line treatment, and they were treated with a second-line chemotherapy [3] or more commonly with a hematopoietic stem cell transplantation (HSCT) [10].

OCs and GnRH Analogues during Therapy

Overall, 12% of the patients received GnRH analogues during chemotherapy; 53% took OCs and 37% nothing. The resumption of menstrual activity was related to the use of the OCs and GnRH analogues during chemotherapy ($p = 0.008$ and 0.034 , respectively). Five patients underwent ovarian tissue cryopreservation, but none of them used it.

Menopausal Status

Menstruation before therapy was regular in 87 patients and irregular in 10 patients. After the end of the therapeutic program, permanent amenorrhea was experienced by 24 women, while 72 women reported resumption of menstrual activity within less than 6 months (mostly within 1–2 months). However, 1 patient experienced 30 months of amenorrhea before resumption of menstrual activity. As for frequency and regularity of menstrual cycles after treatment, these were regular in 63 patients and irregular in 10 patients.

At the time of survey, 34 (35%) women were in menopause. Of these, 9 (26%) experienced a natural menopause, 2 (6%) a surgical menopause (for gynecological reasons), and 23 (68%) iatrogenic menopause (permanent amenorrhea after therapy). Menopause was defined as irreversible amenorrhea lasting more than 12 months.

Excluding the 2 cases of surgical menopause, the average and median age of menopause after treatment was 43.3 and 45.5 years, respectively. Premature menopause (i.e., before 40 years, also known as POF) was experienced by 9% of the women included in our survey (average 34.3 years, median 37 years), whereas early menopause (between ages 40 and 45 years) was noted by 7% of the women (average 43.4 years, median 44 years).

Menopausal Symptoms

Of the 34 women who were in menopause at the time of the interview, 16 (47%) reported hot flashes, 8 (24%) a diagnosis of osteoporosis, 19 (56%) decreased libido, and

14 (41%) mood swings. More than a half experienced more than one symptom (53%), while 7 (21%) did not have any menopausal symptoms.

Decreased libido ($p = 0.028$) and mood swings ($p = 0.024$) were more frequent in women with iatrogenic menopause than in those with natural menopause, while hot flashes and osteoporosis were not associated with the menopause onset modality (natural, surgical, or iatrogenic) ($p = 0.193$ and 0.369 , respectively).

Offspring

Before the diagnosis of lymphoma, 33 women (34%) who answered to the questionnaire already had children, with an average of 1.85 births per woman.

During the follow-up, 40/97 women tried to become pregnant, and only 19% succeeded, with an average of 1.33 births per woman. It should be considered that about half of the patients reported that they had not tried to conceive a child after the treatment for personal reasons.

Prognostic Factors for Amenorrhea after Treatment

Table 1 summarizes the clinical characteristics of the entire population. Using these characteristics, we performed univariate and multivariate analysis to evaluate their role in the occurrence of amenorrhea.

Multivariate analysis revealed that age, R-CHOP, refractoriness, or relapse were associated with the statistically significant high risk of amenorrhea, while the use of OCs significantly reduced the risk of secondary amenorrhea (PR = 0.37; 95% CI 0.17–0.82). Moreover, NHL had an infertility PR of 1.51 at multivariate analysis (95% CI 0.86–2.45) compared to HL (Table 1).

Discussion

This study investigated the risk of infertility, therapy-related amenorrhea, and premature menopause in patients treated with chemo-/radiotherapy for HL and aggressive NHL. We also explored the fertility preservation methods that have been proposed to our patients, in particular the role of pharmaceutical prophylaxis with OCs and GnRH analogues. Most data published on fertility risk and ovarian impairment in lymphoma patients was obtained from patients treated for HL, whereas information on NHL patients is more limited. In our study, we included both HL and NHL patients.

Our study revealed several findings:

1 Age at diagnosis is one of the main determinants of the risk of therapy-induced amenorrhea, with a differ-

Table 1. Univariate and multivariate analysis by clinical characteristics

Characteristic	<i>n</i>	Univariate analysis		Multivariate analysis	
		PR	95% CI	PR	95% CI
Age at diagnosis					
≤26 years	31	1.00	Ref.	1.00	Ref.
27–34 years	30	3.10	0.34–28.49	1.91	0.25–12.90
≥35 years	36	17.22	2.43–122.29	8.21	1.13–45.61
Disease					
HL	61	1	Ref.	1	Ref.
NHL	36	4.56	1.97–11.91	1.51	0.86–2.45
Chemotherapy regimen					
ABVD	60	1.00	Ref.	1.00	Ref.
R-CHOP	20	6.00	2.32–15.54	1.75	0.81–4.07
VACOP-B	6	4.00	0.97–16.48	3.65	1.09–12.19
Other	11	7.64	2.94–19.86	2.42	0.88–6.64
Relapse or progression					
No	81	1.00	Ref.	1.00	Ref.
Yes	16	5.98	3.28–10.91	2.36	1.23–4.78
Radiotherapy					
No	40	1.00	Ref.	1.00	Ref.
Yes	57	0.23	0.10–0.54	0.59	0.67–2.3
OCs before treatment					
No	57	1.00	Ref.	1.00	Ref.
Yes	40	0.86	0.41–1.76	0.87	0.56–1.90
OCs during treatment					
No	46	1.00	Ref.	1.00	Ref.
Yes	51	0.37	0.17–0.82	1.56	0.45–3.21

Ref., reference; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; VACOP-B, etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisolone.

ence of 12.8 years between the mean age at diagnosis of the women who did not resume their menses after therapy and those who did ($p = 0.000$).

2 Amenorrhea was significantly higher in women receiving R-CHOP than in women treated with ABVD (PR = 6.00; 95% CI 2.32–15.54).

3 The resumption of menstrual activity was associated with the use of the OCs and GnRH analogues during chemotherapy ($p = 0.008$ and 0.034 , respectively).

4 Only 19% had children after therapy, with an average of 1.33 births per woman.

5 Premature menopause was experienced by 9% of the women (average 34.3 years, median 37 years), whereas early menopause was noted by 7% of the women (average 43.4 years, median 44 years).

Some reports demonstrated that age at diagnosis is one of the most important risk factors determining secondary amenorrhea and premature menopause [7, 11].

Premature menopause affects 1% of the women under the age of 40 years in the general population [12], but it is

more common among long-term cancer survivors. In our cohort, premature menopause affected 9% of the women, and it was more common in patients with relapsed or refractory disease, as repeated therapies are associated with a significant risk for fertility loss.

Women who experience premature menopause (before age 40 years) or early menopause (between ages 40 and 45 years) have an increased risk of overall mortality, cardiovascular diseases, neurological diseases, psychiatric diseases, osteoporosis, and other sequelae [13].

The medical literature reports that premature menopause is associated with a higher incidence of severe menopausal symptoms. In particular, female patients treated in the HD14 trial of the German Hodgkin Study Group complained of 3 times more severe menopausal symptoms than the control cohort [14].

Meissner et al. [10] studied 46 women treated with CHOP or CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) for aggressive NHL and demonstrated that the last menstrual bleeding oc-

curred significantly earlier in patients when compared with the general population (47 vs. 51 years, $p < 0.0001$). As expected, these women had more severe menopausal symptoms when compared with the general population ($p = 0.0029$).

The chemotherapeutic regimen is an important determinant of the risk of POF. In a EORTC (The European Organisation for Research and Treatment of Cancer) study, women treated for HL with alkylating regimens had an increased risk of POF (60%) when compared with regimens not containing alkylates (3% of POF) [15].

For HL, the standard treatment remains ABVD as it is very rarely associated with POF [10, 16, 17]. A small percentage of patients will relapse, and HSCT may be required even if it is associated with a high risk of POF. For this reason, it is important to discuss the fertility preservation options available before starting the first-line chemotherapy. More intensive regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), in spite of a superior progression-free survival and a significant reduction in the risk of progression compared with ABVD [18], are associated with continuous amenorrhea in more than 50% of the patients [7].

The treatment commonly used for aggressive NHL is R-CHOP or other regimens containing alkylating agents; therefore, POF occurs more often. Moreover, second-line regimens followed by HSCT may be required, and these procedures are also associated with a high risk of POF. This was evident also in our cohort where the CHOP regimen was more toxic than ABVD, as for the development of amenorrhea (PR = 6.00; 95% CI 2.32–15.54).

Of the patients treated for HL, all aged below 40 years at diagnosis, 50% reported post-treatment parenthood [16]. Of the young women treated with CHOP for intermediate- and high-grade NHL, 50% became pregnant during the first complete remission [19], while the pregnancy rate after Hyper-CVAD (hyper-cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, and methotrexate) was 43% [20]. When considering the pregnancy rate reported in the literature, we should consider that not all long-term survivors tried to achieve pregnancy and that the time of follow-up is quite heterogeneous among different studies. In our cohort, only 19% had children after therapy, with an average of 1.33 births per woman. These data are close to the Italian general population (1.4 births per woman) and reflects the rising trend of delaying pregnancy until later in life [21].

The role of OCs in preserving fertility is still a matter of debate. A retrospective study with 405 patients showed

higher amenorrhea rates among women who did not take OCs during therapy [7]. The same authors made a randomized trial that was prematurely ended but they concluded that OCs and GnRH analogues were not useful to protect gonadal function in patients treated with BEACOPP-escalated for HL [22]. No role of OCs was seen in patients treated for osteosarcoma with high-dose ifosfamide, high-dose methotrexate, adriamycin, and cisplatin. However, in these patients, age and the doses of alkylating agents were the most important predictive factors for early menopause [23]. Therefore, a randomized trial to clarify the role of OCs is still warranted.

Blumenfeld et al. [24] investigated the role of GnRH analogues for a total of 2,376 patients by reviewing 29 studies. Among these studies, 20 (5 prospective randomized, controlled trials [RCTs] and 15 non-RCTs) reported a significant decrease in the POF rate among 1,837 survivors using GnRH analogues. The remaining 9 studies (6 RCTs and 3 non-RCTs) did not support a role of GnRH analogues. Despite these opposite results, the authors concluded that the use of GnRH analogues during chemotherapy is recommended in addition to and not instead of in vitro fertilization and cryopreservation of embryos, ova, and ovarian tissue for fertility preservation [24]. We also agree that combining the different available strategies aimed to reduce the risk of gonadal toxicity may increase the odds of preservation of future fertility.

In patients treated for HL with AVBD or ABVD plus BEACOPP, the prophylactic use of GnRH analogues was demonstrated to be a highly significant prognostic factor for fertility preservation (odds ratio = 12.87, $p = 0.001$) [13].

In our study, the resumption of menstrual activity was more frequent among women who used OCs or GnRH analogues during chemotherapy, and these differences were statistically significant ($p = 0.008$ and 0.034 , respectively). Considering that the debate is still ongoing among investigators, the role of OCs and GnRH analogues should be evaluated with prospectively controlled trials.

The resumption of menstrual activity after therapy does not indicate lack of gonadal damage, as gonadal function impairment may manifest as POF or infertility. Although one of the most valid end points for fertility is the number of pregnancies and offspring, it is quite complicated to acquire this information, as many women did not try to conceive for various reasons.

The main limitation of our study is the retrospective analysis; however, it provides clinically important information about the fertility rate and late ovarian function

impairment in long-term HL and NHL survivors, suggesting a possible role of pharmacological prophylaxis with OCs and GnRH analogues.

In conclusion, based on our experience, we suggest counselling with a reproductive specialist who will offer to the patient the best tailored solution to reduce the infertility risk. In particular, patients to require more attention are those receiving CHOP or CHOP-like regimens compared to patients with HL receiving only ABVD.

Statement of Ethics

All subjects gave their written informed consent, and the study protocol was approved by an appropriate ethics committee.

Disclosure Statement

G.A. received honoraria from Roche, Teva, and Takeda. O.A. received honoraria from Celgene, Roche, and Janssen. G.G. received honoraria from Takeda, Celgene, Teva, Pfizer, and Servier. The other authors have no conflicts of interest to disclose.

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