REGULAR ARTICLE

blood advances

Hodgkin lymphoma and female fertility: a multicenter study in women treated with doxorubicin, bleomycin, vinblastine, and dacarbazine

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Key Points

- The number of pregnancies in young women after ABVD treatment for HL is similar to that of controls.
- In addition, 81% of patients who wished to become pregnant after ABVD had at least 1 birth.

Preservation of fertility has become a growing concern in young females with Hodgkin lymphoma (HL). However, the rate of pregnancy after the current most frequently prescribed ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and darcarbazine) chemotherapy for HL has rarely been studied. In this study, we aim to determine the impact of ABVD on the fertility of women treated for HL. We conducted a noninterventional, multicenter study of female patients of childbearing age who were treated for HL. Two healthy apparied women nonexposed to chemotherapy (our controls) were assigned for each patient. Fertility was assessed by the number of pregnancies and births after HL treatment. Sixty-seven patients were included. The median age at diagnosis was 24.4 years (range, 16-43). HL was a localized disease for 68.7%. Of all the patients, 53.7% started at least 1 pregnancy after treatment vs 54.5% of the controls (P = .92). Of all the patients who desired children, 81% had at least 1 pregnancy. Patients treated with ABVD did not have a longer median time to pregnancy (4.8 years in the group of patients and 6.8 years for controls). Across patients, there were 58 pregnancies and 48 births (ratio, 1:2) and 136 pregnancies and 104 births (ratio, 1:3) for the control cohort. No increase in obstetric or neonatal complications has been reported in HL in our study. The number of pregnancies, births, and the time to start a pregnancy in young women treated with ABVD for HL is not different from that of controls. Therefore, females with HL treated with ABVD should be reassured regarding fertility.

Introduction

Hodgkin lymphoma (HL) is a curable lymphoid malignancy most commonly affecting a young population of childbearing age.[1] The long-term complications of HL treatment have become a growing concern, such as those related to radiotherapy (thyroid disorders, breast cancer, and coronary artery disease)

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and those related to intensive chemotherapy (fertility disorders, myelodysplasia, and secondary acute leukemia).

Infertility is one of the major complications in this young population. The opportunity to carry out a parental project at a distance from cancer treatments is an essential part of the quality of life and becomes a real issue for patients, families, and medical teams.[2]

First-line chemotherapy with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) achieves cure rates of ~90%[3] and appears to be not, or only minimally, gonadotoxic.[4-6]

Some retrospective studies have been conducted to assess the long-term fertility of young women treated for HL, with hormonal assays, premature ovarian failure, or amenorrhea (defined as a premature reduction in ovarian reserve, of peripheral origin, occurring before the age of 40) as primary end point.[6,7] Few studies have evaluated the pregnancy or parenthood rates after treatment with ABVD and reported heterogeneous results.[6,9-14] The main objective of our work was to study the impact of ABVD chemotherapy on the fertility of young women treated for HL by measuring the number of pregnancies and births.

Methods

We conducted a retrospective, multicenter cohort exposed/nonexposed study.

Patients

Patients of childbearing age treated with ABVD for HL between 1981 and 2005 were contacted. Patients who received pelvic radiotherapy without previous ovarian transposition were excluded. An information note explaining our study and a paper questionnaire on lifestyle and gynecological and obstetrical history were sent to the departments of hematology. Medical information was collected from the referral physician at the centers of Angers, Nantes, and Poitiers in which the patient was treated or from the Groupe Ouest Est d'étude des Leucémies Aigues et Autres Maladies du Sang database. Patients willing to participate in the study returned the questionnaire to the Clinical Investigation Center of CHU Poitiers. The median follow-up since the inclusion was 4 years. The median follow-up since HL treatment was 12.6 years (range, 6.3-26.7).

Healthy controls

Healthy control participants were selected through the assistance of general practitioners. Two healthy controls were selected for 1 patient each, matched for age, tobacco consumption, body mass index, and geographical area from the established control group.

Assessment of fertility

Fertility was assessed by the number of pregnancies and births. Recovery of regular menstrual cycles and use of medically assisted procreation (MAP) methods were also studied, as was the desire for conception. We have also evaluated other factors affecting fertility, such as gynecological and obstetrical history before chemotherapy, number of children before the diagnosis of HL, and instruction not to procreate for 2 years after the treatment. Hormonal assays and transvaginal ultrasounds were not performed to measure the risk of infertility. Patients did not have treatment with gonadotropin-releasing hormone analogs but could take a contraceptive pill. The primary end point was the number of pregnancies after HL treatment. The secondary end points were the number of births, time to first pregnancy, conception difficulties and use of MAP, and the age of onset of menopause.

Statistical analysis

The pairing was performed using SAS v.9 software (SAS Institute, Cary, NC). Univariate analyses were performed using a McNemar χ^2 test for qualitative variables and a paired sample t test for quantitative variables. We looked at the variables having a prognostic impact on duration before achieving a first pregnancy, such as gynecological history, which may affect fertility. Event occurrence curves were estimated using the Kaplan-Meier method and the comparison of the different risk factors was performed using a log-rank test. Variables with P value <.2 were included in a logistic regression model (ascending Cox model). For all analyses, alpha risk of the first species was set at 5%. Statistical analyses were performed using SPSS software (15.0).

Results

Group characteristics

Characteristics of the cohorts. One hundred and twenty-nine patients were contacted. The global response rate was 52%. Sixty-seven patients answered the questionnaire and were included. One hundred and thirty-four nonexposed controls were included. The characteristics of the patients and nonexposed controls are summarized in Table 1. Median age at diagnosis was 24.4 years (range, 15.6-43.1) in patients and 23.7 years (15.5-42) in controls ($P = .85$). Both groups were homogeneous in terms of body mass index ($P = .91$), tobacco consumption ($P = .157$), and geographic area.

Characteristics of the HL. Ann Arbor stages I, II, III, and IV accounted for 10.4%, 58.2%, 19.4%, and 11.9% of patients, respectively. Forty-six patients received a treatment of "standard" intensity like ABVD. Twenty-one patients received "reinforced" treatment, including 8 with autologous stem cell transplantation (ASCT) and 13 (5 BEACOPP-like [bleomycin, etoposide, epirubicin, cyclophosphamide, vindesine, vinblastine, methotrexate] and 8 VABEM [vindesine, doxorubicin, carmustine, etoposide, methylprednisolone]) without ASCT (Table 2). The median number of cycles of ABVD was 3 (1-5). Sixty-six patients (98.5%) received radiotherapy, including 5 in the pelvic area, all of whom had undergone ovarian transposition before the treatment.

Table 1. Characteristics of patients and controls

Characteristics	Patients, n = 67	Controls, n = 134	P
Age at diagnosis (y), median [minimum-maximum]	24.4 [15.6-43.1]	23.7 [15.5-42]	.85
Body mass index kg/m^2, median [minimum-maximum]	22.3 [16-38]	23.0 [16-38]	.91
Tobacco			
Yes, n (%)	24 (36)	37 (28)	.16
Number of pack-y of cigarettes, median [minimum-maximum]	8 [1-26]	12 [4-37]	
No, n (%)	43 (64)	97 (72)	

Table 2. Description of HL and its treatment

Characteristics	Patients, n = 67
Localized HL, n (%)	46 (68.7)
Disseminated HL, n (%)	21 (31.3)
Standard treatment	
ABVD, n (%)	37 (55.3)
EBVM, n (%)	9 (13.4)
Reinforced treatment without ASCT, n (%)	13 (19.4)
«BEACOPP-like»	5
VABEM	8
Reinforced treatment with ASCT, n (%)	8 (11.9)
ABVD + ASCT	5
Second line + ASCT	3
Radiotherapy, n (%)	66 (98.5)
Number of cycles, median [min-max]	3 [1-5]

EBVM, epirubicin, bleomycin, vinblastine, methotrexate.

Pregnancies of patients before the date of HL diagnosis. Eighteen of the 67 (27%) patients were already mothers of a total of 31 children before starting HL treatment. Difficulties in conception were reported in 33 patients (49.3%) vs 25 controls (18.7%) (P <.001). Only 1 patient had used MAP before HL diagnosis, compared with 7 controls (5.2%) (P = .14). Among all the patients, 12 had gynecological history that might have affected fertility (3 salpingitis, 1 ectopic pregnancy, and 8 had undergone ovarian surgery [ovarian transposition before radiotherapy, ovarian cyst, or endometriosis]). One control had a history of salpingitis, 2 had a known uterine malformation, 3 had an ectopic pregnancy, and 3 had an ovarian or uterine abnormality (cyst, endometriosis, and polyp).

Impact of chemotherapy on fertility

Pregnancies and births after HL. Thirty-six patients (53.7%) started pregnancy after treatment (Table 3) vs 73 controls (54.5%) (P = .92). A total of 58 pregnancies were reported among the 36 patients, compared with 136 pregnancies in 134 controls (P = .2), corresponding to 48 births and 10 interruptions (4 abortions, 5 miscarriages, and 1 medical interruption of pregnancy) in patients vs 104 births (including 3 twin pregnancies) and 35 interruptions (1 abortion, 23 miscarriages, 5 medical interruptions of pregnancy, and 6 ectopic pregnancies) in controls (P = .35). In the ABVD group (n = 37), 20 women (54%) started a pregnancy and 32 pregnancies were reported, corresponding to 26 births and 6 interruptions (3 abortions, 2 miscarriages, and 1 medical interruption of pregnancy) without any difference with the control group (P = .41). In the ABVD group, 81% of patients who wished to become pregnant after HL had at least 1 birth.

The number of pregnancies before HL did not affect the number of pregnancies after HL.

Otherwise, there was no statistically significant difference in the number of pregnancies between the "standard" and "reinforced" treatment groups (48 pregnancies vs 10 pregnancies) (P = .3). Of the 8 patients who received ASCT, 5 had a pregnancy (4 healthy children and 1 abortion).

Table 3. Main results

After the treatment for HL	Patients total N = 67 ABVD n = 37	Controls total N = 134 ABVD matched n = 74	P
Women having started a pregnancy			
ABVD group, n (%)	20 (54)	36 (48)	.59
In the entire cohort, n (%)	36 (53.7)	73 (54.5)	.92
Pregnancies			
ABVD group	32	67	.41
In the entire cohort	58	136	.2
Births			
ABVD group	26	52	.48
In the entire cohort	48	104	.35
Women wanting children who have had at least 1 birth in ABVD group	81%	n.a.	
Median time to pregnancy (y), median (min-max)	4.8 (3.1-6.6)	6.8 (5-8.7)	.21
Difficulty getting pregnant, n (%)	9 (13)	25 (19)	<.001
Use of MAP, n (%)	7 (11)	7 (5)	.125
Age at the onset of menopause (y), median (min-max)	44.4 (36-55)	51.5 (36.2-59)	.006

Time to pregnancy (TTPg). There was no significant difference in TTPg between patients (2 years after treatment) and controls (median of 4.8 years [3.1-6.6] vs 6.8 years [5-8.7], P = .21) (Figure 1). There was no significant difference in TTPg between standard and enhanced treatments (Figure 2).

Pregnancy was advised to be avoided after treatment of HL in 37 patients (55.2%). Recommended durations of avoidance were 6 months for 1 patient, 1 year for 7 patients (10.4%), 2 years for 12 patients (17.9%), and >2 years for 16 patients (23.9%). There was no difference in terms of pregnancy according to the recommended duration of avoidance.

Disturbance of the menstrual cycle. Secondary transient amenorrhea was found in 34 patients (50.7%), with no impact on the number of pregnancies after HL (P = .09), number of total pregnancies (P = .12), difficulties in achieving pregnancy (P = .21), and the use of MAP (P = .24). Definitive secondary amenorrhea increased the use of MAP; of 4 patients, 2 had used MAP (P = .039).

Eleven patients (16.4%) were menopausal (defined by the permanent cessation of menstruation resulting from the loss of ovarian follicular activity) at the time of the latest news compared with 11 controls (8.2%). The median age of onset of menopause in patients was 44.4 years vs 51.5 years in controls (P = .006).

Difficulties in getting pregnant and the use of MAP. Difficulties in getting pregnant were reported by 9 patients (13.4%) vs 25 controls (18.7%) (P = .35). Of the 9 patients who experienced difficulties, 7 reported a negative impact of HL and its treatment (psychological impact of the lymphoma and treatment's side effects), including the 5 patients with ovarian transposition and pelvic radiotherapy, which were significantly associated with difficulties in achieving pregnancy (P = .006) and use of MAP

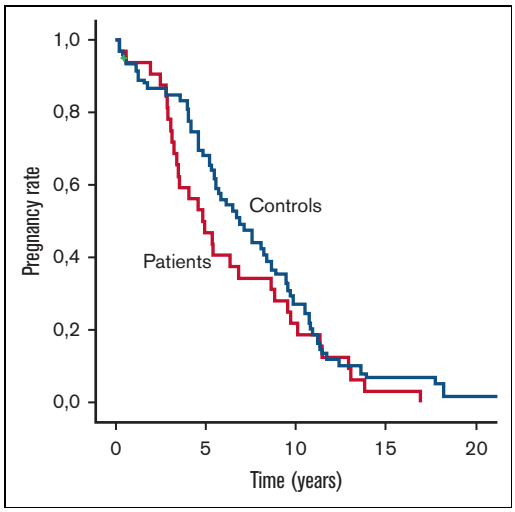

Figure 1. Time to pregnancy in patients and controls. Log-rank test $P = .2$.

($P = .008$). There was no significant difference in use of MAP between patients and controls (7 of 67 [10.5%] vs 7 of 134 [5.2%], $P = .17$).

Impact of lymphoma on the desire for pregnancy. Some patients reported the consequence of lymphoma on their desire to become pregnant in the free comments section of the questionnaire. A negative impact with psychological reasons (stress of cancer, heaviness of treatment and follow-up, and the risk of in vitro fertilization) or practical reasons (for example, the delay of 2 years after HL treatment before pregnancy) was reported by 36% of the patients.

Discussion

This cohort study reports a total of 58 pregnancies (including 48 births) occurring in 36 of 67 female patients (53.7%) previously treated for HL. The number of pregnancies and time to pregnancy

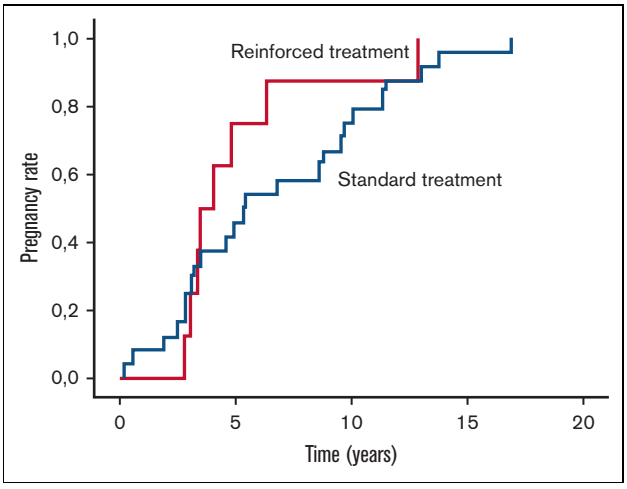

Figure 2. Pregnancy rate in patients with standard and reinforced regimens. Log-rank test $P = .3$.

did not differ from nonexposed controls. Although transient amenorrhea and premature menopause occurred more frequently in patients than in controls, fertility was not affected by HL treatment.

In existing literature, the proportion of women becoming pregnant after HL treatment is heterogeneous and has ranged from 15% to 70%[6,9-15] Regarding the subpopulation of women who expressed their wish to become pregnant, 81% of these patients achieved their objective in our study. This result is quite comparable to that of 75% reported in a study by Van der Kaaij et al.[13] The median time to pregnancy in our study was 4.8 years. It was longer (close to 8 years) in the study by Brusamolino et al[9] although the population had the same median age (24 years). In Hodgson's study,[6] the median time was 2.5 months (range, 1-48 months) but was assessed only for patients wishing to have children and considered only menstruation with no contraception and being sexually active. Another recent Danish study reported parenthood rates generally similar to the general HL population who have not relapsed.[14] Our results and other studies do not support the systematic use of fertility preservation in young patients treated with ABVD for HL,[16] considering the age and the risk of premature ovarian failure,[17] but we systematically recommend a specific consultation for young patients to inform them of the different techniques available,[18] especially because refractory or relapse disease cannot be predicted.

In a population of 562 young women treated for HL in HD13 studies (2 cycles of ABVD), HD14 (4 cycles of ABVD or 2 cycles of ABVD + 2 cycles of BEACOPPesc), and HD15 (6-8 cycles of BEACOPPesc), the birth rate was 6.5% in the BEACOPPesc group vs 15% in the ABVD group.[12] Of the 52% of patients wanting children after treatment with BEACOPPesc, only 15% achieved this after a 4-year follow-up. In another study of a German group, treatment with BEACOPPesc led to amenorrhea in 51% of cases.[8] In our study, of the 5 patients treated with a BEACOPP-like regimen (without procarbazine, which was replaced with methotrexate and vinblastine), 5 had transient amenorrhea during treatment, 2 had definitive secondary amenorrhea, and 4 were menopausal at the end date. None of these 5 patients achieved pregnancy after treatment. Two women were already mothers of 2 children each, 2 had no desire for children after HL, and 1 woman who wanted children but had undergone ovarian transposition had difficulties getting pregnant and used MAP, which was unsuccessful. However, given the small number of this group of patients, it is not possible to make a definitive conclusion. On the other hand, a German study showed that the motherhood rates of the main analysis set across 5 different age groups were comparable with the representative data of the German general population in patients receiving a maximum of 2 BEACOPPesc.[17]

This was a retrospective study based on patient participation. Potential selection bias cannot be ruled out, as well as a recall bias because of the use of a questionnaire. The response rate was 52%. Patients who had difficulty conceiving may not have been willing to participate in the study. Our results could be overestimated by looking only at the proportion of patients who responded to treatment and completed their parenthood project. The size of the population treated was limited and the treatments were not identical because 37 patients were treated with ABVD, whereas 9 received "ABVD-like" treatment, and 21 patients received "reinforced" treatment. However, the group of 37 patients

treated with ABVD allows comparison with other studies. Moreover, our study provided information on fertility in the group of 21 women who were more heavily treated. In particular, we report 5 pregnancies in 5 patients (including 4 healthy children) after ASCT of 8 patients, which is uncommon.[19]

The strengths of our study are its multicentric nature, the use of a strong primary end point (number of pregnancies), a long follow-up period, and comparison with matched controls. Numerous studies have focused on the evaluation of female fertility, but mainly by an indirect method of hormonal assays coupled with ovarian ultrasound or indirect criteria such as the occurrence of amenorrhea. The number of pregnancies and the number of births are concrete data that can easily be discussed with patients in daily practice. It is easy for patients to understand that their chances of getting pregnant are not different from those of controls.

Finally, we have access to data on quality of life via "free comments" that women could write on the returned questionnaire. These comments are representative of real life. If patients do not start pregnancies after HL treatment because they do not want children, it is not infertility. Forty percent of patients reported that HL treatment had no impact on their desire to conceive a child; 36% had a negative impact: psychological reasons were given for some (especially the heaviness of treatment and follow-up, risk of in vitro fertilization) or practical reasons for others (eg, pregnancy was not recommended for 2 years after HL treatment). They also reported the difficulty of fertility preservation, the heaviness of this care, and its psychological impact.

These results are in adequation with other studies[20] that reported that the desire to have children would be reduced to 77% among young cancer survivors compared with 90% in the general population of the same age,[21] because of psychological difficulties in planning the future with the risk of relapse,[22,23] psychological complications due to a negative impact on sexual life for two-thirds of patients, especially with early menopause,[24] and fewer marriages among cancer survivors.[25]

In this study, we found that the number of pregnancies in young women after ABVD treatment for HL is similar to that of the general population, thereby confirming the low female gonadotoxicity of this chemotherapy regimen. However, even in patients with localized HL for whom the use of techniques for fertility preservation might not be necessary, because of the risk of relapse and escalation of therapy, we recommend a specific consultation because young patients should be informed about the risks of infertility and fertility preservation techniques.

Authorship

Contribution: A.M., C.P., and S.G. wrote the manuscript and all other authors helped in collecting the data and approved the final version of the manuscript.

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