Premature Ovarian Failure and Fertility in Long-Term Survivors of Hodgkin's Lymphoma: A European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Étude des Lymphomes de l'Adulte Cohort Study

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ABSTRACT

Purpose

In this large cohort of Hodgkin's lymphoma survivors with long follow-up, we estimated the impact of treatment regimens on premature ovarian failure (POF) occurrence and motherhood, including safety of nonalkylating chemotherapy and dose-response relationships for alkylating chemotherapy and age at treatment.

Patients and Methods

The Life Situation Questionnaire was sent to 1,700 women treated in European Organisation for Research and Treatment of Cancer and Groupe d'Étude des Lymphomes de l'Adulte trials between 1964 and 2004. Women treated between ages 15 and 40 years and currently not using hormonal contraceptives ($n = 460$) were selected to assess occurrence of POF. Cumulative POF risk was estimated using the life-table method. Predictive factors were assessed by Cox regression analysis.

Results

Median follow-up was 16 years (range, 5 to 45 years). Cumulative risk of POF after alkylating chemotherapy was 60% (95% CI, 41% to 79%) and only 3% (95% CI, 1% to 7%) after nonalkylating chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine; epirubicin, bleomycin, vinblastine, and prednisone). Dose relationship between alkylating chemotherapy and POF occurrence was linear. POF risk increased by 23% per year of age at treatment. In women treated without alkylating chemotherapy at age younger than 32 years and age 32 years or older, cumulative POF risks were 3% (95% CI, 1% to 16%) and 9% (95% CI, 4% to 18%), respectively. If menstruation returned after treatment, cumulative POF risk was independent of age at treatment. Among women who ultimately developed POF, 22% had one or more children after treatment, compared with 41% of women without POF.

Conclusion

Nonalkylating chemotherapy carries little to no excess risk of POF. Dose-response relationships for alkylating chemotherapy and age at treatment are both linear. Timely family planning is important for women at risk of POF.

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INTRODUCTION

High cure rates (80% to 90%) of Hodgkin's lymphoma (HL) and a predominant incidence in patients age 20 to 44 years have resulted in many patients wishing to start or complete a family after treatment.¹⁻³ Since 1964, the European Organisa-

tion for Research and Treatment of Cancer (EORTC) Lymphoma Group (in collaboration with the Groupe d'Étude des Lymphomes de l'Adulte [GELA] since 1993), has treated patients with HL uniformly in clinical trials. From 1982 onward, the aim of these trials has also focused on reduction of treatment-related toxicity.

Whereas in men fertility is relatively easily studied by analysis of sperm counts and follicle stimulating hormone,^{4,5} hormone measurements in women are influenced by menstrual cycle patterns and hormonal contraceptive use. Pregnancy outcomes and documentation of (premature) cessation of menses offer reliable information. Premature ovarian failure (POF), defined as irreversible amenorrhea lasting more than 12 months before the age of 40 years, can develop during treatment or occur years later, reflecting early depletion of oocytes caused by gonadotoxic treatment. Interaction between the gonadotoxic drug and menstrual cycle in women can be complex as regards time. Women may cease menstruating during therapy, recover thereafter, and become pregnant but still experience POF or early menopause (between ages 40 and 44 years) later on.⁶

Few reports on ovarian failure and infertility after treatment for HL have provided long-term follow-up.^{7,8} Most have involved low patient numbers or women treated in childhood.⁸⁻¹⁰ Information on both menstrual status and number of children is even rarer. In addition, almost no data have been published on nonalkylating chemotherapy, which is presently considered first-choice therapy in early-stage disease.⁹ In 2009, the Life Situation Questionnaire (LSQ) was sent to HL survivors treated within EORTC-GELA trials. This questionnaire addressed in detail fertility and parenthood. It offered the opportunity to study fertility outcome in a large cohort of long-term survivors and compare the influence of various treatment regimens on POF occurrence and age at menopause as well as on female fertility by comparing chances of motherhood after HL.

PATIENTS AND METHODS

Women

Overall, 3,020 women were included in nine consecutive randomized clinical trials conducted in 13 European countries between 1964 and 2004 (Table 1). Protocols of the H1 through H9 trials are detailed in published reports.^{2,11-19} Patients presented with histologically proven, previously untreated HL. Exclusion criteria were concomitant or previous malignancies or serious comorbidities. Treatment administered was recorded prospectively, including chemotherapy type, number of cycles, radiotherapy field, and dose. In 2008, after human investigations committee approval, current addresses were tracked for all 2,712 women alive at last follow-up. For 1,700 women from five countries and 114 hospitals, a recent address was obtained (Fig 1).

Questionnaire

The LSQ addresses issues not yet available in any validated questionnaire. It contains the following items: parenthood after HL; education, work, and insurance; health and social situation; and support received during treatment. Occurrence of menopause was evaluated based on the following question: "At this moment, do you have a menstrual cycle? If no, is this because of a) menopause b) removal of uterus and/or ovaries c) pregnancy or breastfeeding d) continuous contraceptive use or e) other, please specify." Age at last menstruation was also recorded, including whether this last menstruation was more than 1 year ago. Occurrence of immediate menopause during treatment was evaluated based on the following question: "During first treatment for Hodgkin's lymphoma, did you have a spontaneous menstrual cycle? If no, did your menstrual cycle spontaneously return after treatment?" In the LSQ, data on embryo, oocyte, and ovarian cryopreservation were collected. However, none of these options had resulted in any live births among our patient group.

Of 1,700 women approached, 964 (57%) returned the questionnaire and provided written informed consent. A nonresponder analysis performed to compare those who did not reply with those who did indicated almost no differences. Responders came more often from earlier trials and thus were slightly less often treated with nonalkylating chemotherapy and radiotherapy

above the diaphragm. Disease stage distribution was similar in responders and nonresponders.

Selection of Women

For the POF analysis, we included all women age 15 years or older at treatment who had completed the questions on menstruation and menopause ($n = 945$). Women who were (post) menopausal before treatment were excluded, as were those with unknown menstrual status because of current contraceptive use. Women who had had sterilizing surgery (removal of uterus and/or ovaries) at an unknown date and women with menopause resulting from an unrelated medical event were also excluded.

Because only effects of primary treatment were considered, women with nonresponse or progression during treatment were excluded; those who experienced a relapse were censored at time of relapse. Rates of progression or relapse were low (82 of 964 patients; 8.5%). Women with a second malignancy were censored at time of that diagnosis, as were those with surgical menopause at time of surgery and those with continuous progestagen use at start of use, if dates were provided. Analysis was performed on treatment actually received, not on an intention-to-treat basis. Sixteen women received several chemotherapy regimens (protocol violation) and were excluded from analysis. After exclusions, 575 women were suitable for analysis; 460 were younger than 40 years of age at treatment for HL and therefore at risk for POF. They were included in analyses with POF as the end point (Fig 1).

Definitions

POF was defined as menopause before age 40 years. Menopause was defined as cessation of menstruation at least 1 year before the date of the survey in the absence of pregnancy, breastfeeding, continuous use of progestagens or other medication causing amenorrhea, or surgical removal of uterus and/or ovaries.

Women administered chemotherapy were grouped into those treated with regimens without alkylating agents (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]²⁰; epirubicin, bleomycin, vinblastine, and prednisone [EBVP]²¹) and those treated with alkylating chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone [MOPP]²²; MOPP/doxorubicin, bleomycin, and vinblastine [MOPP/ABV hybrid [RSQB]²³; cyclophosphamide, doxorubicin, vincristine, bleomycin, etoposide, procarbazine, and prednisone [standard BEACOPP]²⁴). Of all women included, 11% to 12% received ABVD, 18% to 19% received EBVP, 6% received MOPP, 33% to 36% received MOPP/ABV, and 4% received standard BEACOPP. None received dose-escalated BEACOPP (Appendix Table A1, online only). Cycles administered at reduced doses were considered full cycles. The number of cycles was used to estimate the amount of alkylating chemotherapy administered, counting one cycle of MOPP/ABV or BEACOPP as equivalent to 0.5 MOPP cycle. In two trials, maintenance chemotherapy for 2 years was administered: vinblastine 10 or 6 mg, or 6 mg weekly for 3 months alternating with procarbazine daily 150 mg for 3 weeks, with a gap of at least 4 weeks in between.^{11,12} Because the cumulative procarbazine dose in this regimen was 9 g/m², approximately comparable to six MOPP cycles, procarbazine-containing maintenance therapy was considered equivalent to six cycles of MOPP.

Information on smoking, education level, and number of biologic and adopted children was obtained from the LSQ questionnaire. Education level was grouped into low, middle, and high: low comprised primary school and the lower level of secondary school (corresponding to International Standard Classification of Education [ISCED] levels²⁵ 0, 1, and 2); middle, the higher levels of secondary school (ISCED levels 3 and 4); and high, higher education and university (ISCED levels 5 and 6).

Statistical Analysis

The aim of this study was to estimate the impact of HL treatment regimens on POF occurrence (primary end point), menopause, and motherhood. A cohort analysis was performed. Women were observed from start of HL treatment until POF ($n = 77$), age 40 years ($n = 202$), relapse ($n = 39$), second malignancy ($n = 8$), surgical menopause ($n = 4$), first continuous progestagen use ($n = 10$), or date of LSQ completion if younger than 40 years and still menstruating ($n = 120$).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Replied to LSQ				All Women Included in H1 to H9 Trials	
	Included in Analysis		Excluded From Analysis			
	No.	%	No.	%	No.	%
No. of women	575	19*	389	13*	3,020†	
Country						
France	204	35	192	49	1,409	47
the Netherlands	311	54	159	41	1,037	34
Belgium	46	8	28	7	315	10
Italy	14	2	9	2	102	3
Other	0	0	1	< 1	157	5
Age at treatment start, years						
Median	30		27		29	
Range	15-56		10-70		6-71	
15-24	192	33	169	43	1,054	35
25-34	195	34	109	28	976	32
35-44	137	24	44	11	529	18
≥ 45	51	9	67	17	461	15
Unknown	0	0	0	0	1	< 1
Age at LSQ reply, years						
Median	49		40		NA	
Range	25-76		24-84		NA	
Follow-up duration, years						
Median	15		12		NA	
Range	5-45		5-45		NA	
Period of treatment						
1964-1976‡	42	7	6	2	242	8
1977-1993§	217	38	97	25	1,117	37
1994-2004	316	55	286	74	1,661	55
Disease stage						
I, II	514	89	344	88	2,685	89
III, IV	61	11	45	12	335	11
B symptoms						
Absent	405	70	277	71	2,084	69
Present	159	28	105	27	853	28
Unknown	11	2	7	2	83	3
Initial treatment						
Chemotherapy	456	79	351	90	2,353	78
No alkylating agents	192	33	160	41	933	31
Alkylating agents	264	46	191	49	1,410	47
Unknown	0	0	2	< 1	10	< 1
Radiotherapy	541	94	349	90	2,738	91
Above diaphragm	405	70	286	74	1,963	65
Below diaphragm	136	24	63	16	772	26
Unknown	0	0	0	0	3	< 1
Staging laparotomy	40	7	4	1	230	8
Ovarian transposition	7	1	1	< 1	66	2
Second-line treatment	53¶	9	29	7	507	17
Second malignancy	18	3	10	3	135	4
Smoking						
Never	299	52	216	56	Not known	
Ever	274	48	169	43		
Unknown	2	< 1	4	1		
Education level						
Low	155	27	114	29	Not known	
Middle	183	32	126	32		
High	228	40	141	36		
Unknown	9	2	8	2		

NOTE. Because of rounding, percentages may exceed or fall short of 100%.

Abbreviations: LSQ, Life Situation Questionnaire; NA, not applicable.

*Percent of all women eligible.

†All women who were deceased, did not respond, and were lost to follow-up included.

‡Comprises H1 (n = 21) and H2 (n = 21) trials.

§Comprises H5 (n = 30), H3B4 (n = 11), H6 (n = 64), and H7 (n = 81) trials; first part of H34 trial (n = 24); and start of H8 trial (n = 8).

||Comprises second part of H34 trial (n = 27) and H8 (n = 133) and H9 (n = 156) trials.

¶Observations censored at time of relapse or second malignancy, unless menopause occurred before relapse or second malignancy.

Fig 1. CONSORT diagram; selection of women included in analysis. (*) Menopause after thyroid problems, curettage (Asherman's syndrome), syndrome of Mayer-Rokitansky-Küster, cerebrovascular accident, and endometriosis (one patient case in each category).

Time to POF was defined as time from start of treatment to POF occurrence, to age 40 years, or to LSQ reply, whichever came first. Cumulative risks of POF and exact binomial 95% CIs were estimated using the life-table method.²⁶ Univariable analysis of factors influencing POF occurrence and menopause age was performed using the Kaplan-Meier method and log-rank test. A multivariable analysis of prognostic factors with regard to POF occurrence was performed using Cox regression analysis. Variables entered into the model were treatment age; chemotherapy (alkylating, nonalkylating) or cycles of alkylating chemotherapy in MOPP equivalents (no alkylating chemotherapy, < four cycles of MOPP equivalent, ≥ four cycles of MOPP equivalent); radiotherapy (above or below diaphragm or on iliac region); second-line treatment (no, yes); treatment period (1964 to 1976, 1977 to 1993, 1994 to 2004); clinical stage (I to II, III to IV); presence of B symptoms (no, yes); smoking (never, ever); and

education level (low, middle, high). A stepwise selection procedure was used. The likelihood ratio test was used to compare a model with age or cycles of MOPP equivalent as continuous variables against models with age or cycles of MOPP equivalent as dichotomous, categorical, logarithmic, or continuous quadratic variables (results shown in part). By receiver operating characteristic analysis, the optimal cutoff for treatment age was evaluated in predicting POF occurrence. Exact binomial 95% CIs for sensitivity and specificity were calculated. All statistical tests were two sided, and statistical significance was defined as a *P* value of less than .01 to adjust for multiple comparisons.

RESULTS

Characteristics for all women included in the trials (*N* = 3,020) and those selected for analysis are listed in Table 1 (*n* = 575) and Table 2 (selection POF, *n* = 460). Women selected were more often treated 10 or more years ago, because the menstrual status of women using hormonal contraceptives (on average younger) could not be evaluated. Women selected for analysis of POF were on average younger at treatment because those age 40 years or older were no longer at risk for POF. Clinical stage distribution was similar in the groups.

After median follow-up of 16 years (range, 5 to 45 years), 77 of 460 women developed POF. To avoid overestimation of POF incidence compared with general population data, we hypothesized all women excluded from analysis because of use of hormonal contraceptives still had a menstrual cycle. Being younger, these women were more probably fertile than those who did not use hormonal contraceptives. Under this most conservative approach possible, the corrected incidence of POF in our cohort was 20.1% (95% CI, 15.9% to 24.8%) compared with 0.9% (95% CI, 0.3% to 1.5%) in the general population.²⁷

Twenty-three percent of women were treated with radiotherapy alone (of whom one received iliac radiotherapy), 33% with combined chemoradiotherapy without alkylating agents and 44% with combined radiotherapy and alkylating agents. The distribution of treatment and other characteristics according to POF occurrence is shown in Table 2. Sixty-nine (34%) of 202 women treated with alkylating chemotherapy developed POF, whereas among women treated with nonalkylating chemotherapy, four (3%) of 151 did. Among women treated with iliac-region radiotherapy, 11 (41%) of 27 had POF, but all had also been treated with alkylating chemotherapy.

Multivariable Analysis

Figures 2A to 2D illustrate treatment (alkylating chemotherapy, yes or no) and treatment age influence on age of menopause. Women treated with alkylating chemotherapy had an age-adjusted hazard ratio (HR) of 12.31 (95% CI, 5.90 to 25.68; *P* < .001) for POF occurrence compared with women not treated with alkylating chemotherapy (Table 2). The cumulative risk of POF for treatment with alkylating chemotherapy (*n* = 202) was 60% (95% CI, 41% to 79%) and only 3% (95% CI, 1% to 7%) or 6% (95% CI, 2% to 20%) for treatment with nonalkylating chemotherapy (ABVD or EBVP, *n* = 151) or radiotherapy only (*n* = 107), respectively. The adjusted HRs were 9.84 (95% CI, 4.62 to 20.97; *P* < .001) for women treated with fewer than four cycles of MOPP-equivalent chemotherapy and 21.10 (95% CI, 9.49 to 46.93; *P* < .001) for

Table 2. Patient Characteristics in Relation to Presence of POF

Characteristic	Total		POF		No POF		<i>P</i> *	Model With All Variables			Final Model		
	No.	%	No.	%	No.	%		HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
No. of women	460		77	17†	383	83†							
Age at start of treatment, years							< .001	1.23‡	1.16 to 1.30	< .001	1.23‡	1.16 to 1.30	< .001
15-24	192	42	14	18	178	46							
25-34	195	42	44	57	151	39							
35-39	73	16	19	25	54	14							
Treatment period							.004						
1964-1976	42	9	1	1	41	11		1.00			—		
1977-1993	188	41	43	56	145	38		1.80	0.22 to 15.05	.59			
1994-2004	230	50	33	43	197	51		1.52	0.18 to 13.02	.70			
Disease stage							< .001						
I, II	409	89	54	70	355	93		1.00			—		
III, IV	51	11	23	30	28	7		1.32	0.68 to 2.56	.41			
B symptoms							< .001						
Absent	323	70	36	47	287	75		1.00			—		
Present	130	28	40	52	90	24		1.32	0.80 to 2.17	.27			
Unknown	7	1	1	1	6	2							
Initial treatment													
Chemotherapy	353	77	73	95	280	73	< .001						
No alkylating agents	151	33	4	5	147	38		1.00			1.00		
Alkylating agents§	202	44	69	90	133	35	< .001				12.31	5.90 to 25.68	< .001
1.5 to three cycles of MOPP equivalent	155	34	44	57	111	29		8.49	3.75 to 19.23	< .001	9.84	4.62 to 20.97	< .001
≥ Four cycles of MOPP equivalent	47	10	25	29	22	6		15.04	6.14 to 36.87	< .001	21.10	9.49 to 46.93	< .001
Radiotherapy	429	93	69	90	360	94	< .001						
Above diaphragm	319	69	53	69	266	69		1.00					
Below diaphragm, not iliac region	83	18	5	6	78	20		0.83	0.32 to 2.16	.70			
Iliac region	27	6	11	14	16	4	< .001	0.76	0.35 to 1.66	.49			
Smoking							.186						
Never	237	52	35	45	202	53		1.00			—		
Ever	222	48	42	55	180	47		0.86	0.54 to 1.38	.54			
Unknown	1	< 1	0	0	1	< 1							

NOTE. Because of rounding, percentages may exceed or fall short of 100%.

Abbreviations: HR, hazard ratio; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; POF, premature ovarian failure.

*Log-rank test.

†Percent of all women included.

‡Age analyzed as continuous variable.

§Either alkylating agents as dichotomous (yes or no) or categorical variable (no alkylating agents, 1.5 to three cycles of MOPP equivalent, ≥ four cycles of MOPP equivalent) were entered into multivariable model; difference between chemotherapy without alkylating agents and radiotherapy only was not statistically significant.

||Radiotherapy on iliac region (no or yes) and combination variable of radiotherapy and alkylating chemotherapy (no alkylating chemotherapy and no radiotherapy below diaphragm, radiotherapy below diaphragm but no alkylating chemotherapy, alkylating chemotherapy but no radiotherapy below diaphragm, or both) were not statistically significant.

women treated with four or more cycles compared with those treated without alkylating chemotherapy (Table 2). Number of cycles of MOPP equivalent (categorical) was highly significant ($P < .001$) when entered into the Cox regression model for POF risk, which included only women treated with alkylating chemotherapy, indicating a significant dose-response relationship (Fig 3). Comparing the model with cycles of MOPP equivalent as continuous variable against the model with cycles of MOPP of equivalent as quadratic or logarithmic variable showed no statistically significant difference ($P = .92$ and $P = .30$, respectively), indicating a linear dose-response relationship. The HR per cycle of alkylating chemotherapy was 1.50 (95% CI, 1.37 to 1.64; $P < .001$).

There was a 23% increase in POF risk per year of age at treatment (Table 2). Comparing the model with treatment age as continuous variable against the model with treatment age as quadratic or logarithmic variable showed no statistically significant difference ($P = .16$ and

$P = .19$, respectively), indicating a linear relationship. However, when actual calendar age attained at end of follow-up was used as a time variable in survival analysis, the difference between age groups at treatment was much smaller. The total cumulative risks of POF were 17% (95% CI, 9% to 30%) for those younger than age 25 years at treatment and 32% (95% CI, 20% to 47%) for those 35 years of age or older, respectively, but the difference was mostly the result of direct menopause during treatment ($n = 94$). If only women with recurring menstruation after treatment were included, the cumulative risks of POF were 17% (95% CI, 9% to 30%) and 16% (95% CI, 7% to 35%), respectively. This illustrates that with long-term follow-up, women without direct acute ovarian failure at time of treatment had a comparative cumulative risk of developing POF, regardless of treatment age.

We further evaluated prognostic value of treatment age for POF occurrence by calculating receiver operating characteristic curves for

Fig 2. Time to menopause after treatment for Hodgkin's lymphoma by age at start of treatment: (A) 15 to 24, (B) 25 to 34, (C) 35 to 44, and (D) 45 years or older. Alk+, chemotherapy containing alkylating agents with or without radiotherapy ($n = 264$); Alk-, chemotherapy not containing alkylating agents with or without radiotherapy or radiotherapy alone ($n = 311$).

several cutoff values. The effect of age on POF occurrence was smaller in women treated with alkylating chemotherapy (area under the curve, 0.75; 95% CI, 0.54 to 0.96) compared with women treated without alkylating chemotherapy (area under the curve, 0.68; 95% CI, 0.61 to 0.76; Figs 4A, 4B). In the latter, the best cutoff value was treatment before age 32 years versus treatment at a later age. Sensitivity was 88% (95% CI, 83% to 91%) and specificity was 71% (95% CI, 65% to 77%). For a cutoff at age 30 years (cutoff usually selected in literature), specificity was 63% (95% CI, 57% to 69%). We found no statistically significant interaction between treatment age as continuous ($P = .18$) or categorical variable ($P = .61$) and the number of cycles of MOPP equivalent as categorical variable. The cumulative risks for POF in women treated at age younger than 32 years and age 32 years or older without alkylating chemotherapy were 3% (95% CI, 1% to 16%) and 9% (95% CI, 4% to 18%), respectively. The HR for POF associated with age 32 years or older at treatment was 15.65 (95% CI, 1.88 to 130; $P = .01$) compared with age younger than 32 years in women treated without alkylating chemotherapy. Other possible risk factors for POF were also assessed. Smoking, B symptoms, clinical

stage, and period of treatment had no significant influence on POF occurrence (Table 2).

Overall, 94 women developed acute menopause during first-line treatment: none, 14 (15%), 41 (44%), and 39 (41%) when ages 15 to 24, 25 to 34, 35 to 44, and 45 years or older, respectively. Sixty-four women (68%) were treated with alkylating chemotherapy. Of 77 women who developed POF, 17 (22%) had at least one biologic child after treatment; nine were treated before age 25 years, and eight were from 25 to 32 years of age. This must be compared with 124 (41%) of 300 of women without POF who had at least one biologic child after treatment.

DISCUSSION

To our knowledge, this is the first large study to evaluate POF occurrence based on data provided by women themselves, with treatment administered in prospective clinical trials and without masking through contraceptive use. The results highlight several major facts.

Fig 3. Cox regression estimation of probability of patients free of premature ovarian failure (POF) by time interval since chemotherapy (censored at age 40 years) in 460 women treated for Hodgkin's lymphoma by dose of alkylating chemotherapy, adjusted for age at treatment. MOPP, mechlorethamine, vincristine, procarbazine, and prednisone.

First, we showed nonalkylating chemotherapy carries little excess risk of POF. However, even in this treatment group, chemotherapy administered in women age 32 years or older resulted in an elevated risk of POF development (9% v 0.9% in general population). Second, POF occurrence is mainly influenced by alkylating chemotherapy use; the dose relationship between alkylating chemotherapy and POF occurrence is linear. Finally, we can offer insight into the influence of treatment-related POF on motherhood.

The emerging use of (dose-escalated) BEACOPP seems to represent a step backward compared with ABVD from the fertility viewpoint. Behringer et al²⁸ found levels of acute menopause during treatment of 32% after BEACOPP baseline, 55% after COPP/ABVD, and even 67% after escalated BEACOPP. Escalated BEACOPP contains almost double the cyclophosphamide dose and the same procarbazine dose as BEACOPP, so two cycles of escalated BEACOPP can be roughly equated to 1.5 cycles of MOPP, resulting in an HR for POF of 9.84.

We confirmed the dose-response relationship for procarbazine found by De Bruin et al⁷ in a study based on medical records not excluding oral contraceptive use. They found an HR of 12.3 for POF after chemotherapy (any type), whereas no significant effect was observed for nonalkylating chemotherapy, used in 50 of 331 women only. The rare reports documenting the effect of nonalkylating chemotherapy on fertility concern limited numbers (24 to 70 women) and sparse data.^{9,29-31}

Our data show an increase in risk of POF of 23% per year of age at treatment (HR, 1.23), corrected for dose of alkylating chemotherapy administered. The prognostic value of treatment age for POF occurrence is most pronounced in women receiving nonalkylating chemotherapy. The cutoff age found (32 years) is close to that generally used (30 years).

A disadvantage, but simultaneously a strength, of our analysis concerns the information on women currently using hormonal contraception, who had to be excluded because ongoing menstruation

Fig 4. Receiver operating characteristic curves for premature ovarian failure occurrence by treatment age for women treated (A) without and (B) with alkylating chemotherapy.

could mask menopause. A consequence of excluding these on average younger and probably more fertile women is that POF incidences might be inflated. In the comparison with POF incidence in the general population, this has been corrected by using the most conservative estimate possible, assuming that all hormonal contraception users are still menstruating.

Our results are based on a questionnaire filled in by women treated under clinical trial conditions. Correct and current information on menstrual status is best obtained from women themselves, not

from medical records. However, every questionnaire-based study suffers from response bias. In our study, responders differed slightly from nonresponders in the treatment received but not in treatment age or disease stage. No information on education level was available for nonresponders.

In any survival analysis, the question of censoring is important. In our study, limited numbers were censored because of relapse, second malignancy, or other reasons, so censoring probably did not influence the study results.

Our report is among the few to offer information on the impact of POF on motherhood. Despite treatment toxicity experienced, fortunately, one fourth of women delivered one or more children before POF occurrence. Conversely, our report also indicates that women with proven fertility after treatment can still be confronted with infertility problems at a later stage.

In summary, women treated with nonalkylating chemotherapy younger than 32 years of age have little to no excess POF risk. Alkylating chemotherapy carries a serious POF risk, with HRs of 10 to 21, depending on dose administered. Women with recurring menstruation after treatment should be informed about their potentially shortened fertility lifespan.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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