Parenthood in long-term survivors after CHOP with or without etoposide treatment for aggressive lymphoma

We read with great interest the report of Greaves et al (2013) regarding patient-perceived fertility and sexual function in long-term survivors of haematological malignancy. The authors describe a lower cumulative fertility rate in female patients than in the matched general population as well as a negative impact of cancer on sexual function. We agree with their conclusion that all patients should be advised of the potential late effects of treatment on fertility.

However, as different treatment regimens are associated with varying degrees of gonadal toxicity, the patient should be informed of the risks that are related to the specific regimen (Loren et al, 2013). To complement the report of Greaves et al (2013), we would like to share our results of a retrospective analysis on the side effects on fertility in patients with aggressive non-Hodgkin lymphoma (NHL) who received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone) as primary therapy. Only a few studies have been performed on the adverse effects of chemotherapy for aggressive NHL on fertility (Grigg, 2004; Leader et al, 2011), most of which included small numbers of patients, employed heterogeneous chemotherapy regimens or covered short follow-up periods. Whereas CHOP as a standard regimen for aggressive lymphoma is supposed to be associated with only temporary side-effects on fertility, nothing is known about the effect of intensification of CHOP, e.g. by adding etoposide in regimens such as CHOEP (Pfreundschuh et al, 2004) or dose-dense EPOCH (Wilson et al, 2002), or of dose-dense chemotherapy.

Our study assessed fertility aspects in young patients who were in continuous first remission after treatment in two large prospective multicentre trials, the Mabthera International Trial (Pfreundschuh et al, 2006), and the German High-Grade Non-Hodgkin’s Lymphoma Study Group NHL-B1 study (Pfreundschuh et al, 2004), between 1995 and 2003. We focused on parenthood to assess fertility in our patient group, as infertility is defined as the inability of a couple to conceive. Surrogate indicators, such as regular menstruation cycles or hormone levels alone could provide only incomplete information. Long-term survivors of both studies were invited to respond to a questionnaire approved by the local ethics committee. Informed consent was obtained from all responders. Patients who received radiotherapy to the gonadal area as part of their primary treatment were excluded from the analysis.

A total of 101 patients (median age at treatment initiation 32 years, median follow-up after treatment completion 12 years) agreed to participate in the survey [response rate of 53.1%; comparable to the report of Greaves et al (2013)]. Within the respondents (46 female, 55 male), 48 patients already had children before lymphoma treatment (Table I). Forty-nine patients expressed an explicit wish to have children after treatment (17 female, 32 male). Thirteen of these 49 patients made no active attempt to reproduce despite their wish to have children, with lack of appropriate partner (six patients) and fear of lymphoma relapse (three patients) being the main reasons. Of the remaining 36 patients (13 female, 23 male) who made active attempts to reproduce, 26 (10 female, 16 male) achieved their goals, all without use of assisted reproduction technology. Apart from three deliberate abortions, all pregnancies were uncomplicated and resulted in a total of 40 live births. The results in the subgroup of patients who received CHOEP instead of CHOP were similar to those in the whole study group. In detail, 36 (15 female, 21 male) of 67 (32 female, 35 male) patients treated with CHOEP expressed a wish to reproduce after chemotherapy. Of these, 25 (12 female, 13 male) actively attempted to reproduce and 19 (10 female, nine male) finally succeeded, resulting in 25 live births overall. Within the subgroup of patients who were treated with a 2-week regimen, three of three female and six of eight male patients with a desire for parenthood were successful.

Comparison of patient data with the German general population [The German Socio-Economic Panel Study (Schmitt, 2005)] revealed no difference in the overall percentage of childless women (21.7%) in the study population versus comparable age-groups of the general population [20.8%, binomial test, 95% confidence interval (CI), 0.109–0.364; P = 0.8563]. The percentage of childless male study patients (41.8%) tended to be higher than that of childless men in the general population (32.6%). This statistically insignificant difference (95% CI, 0.287–0.559; P = 0.1516) was largely a consequence of low rates of pre-treatment parenthood and attempted post-treatment parenthood in our patients and only to a minor degree due to involuntary post-treatment childlessness. The extent of childlessness in our patient population therefore seemed to result rather from personal choice and psychosocial reasons than from chemotherapy-induced gonadal toxicity. Similar results have been reported for Hodgkin lymphoma survivors (van der Kaaij et al, 2012) with
Table I. Results.

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<th>All patients</th>
<th>Female CHOP patients</th>
<th>Male CHOP patients</th>
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<td>All patients</td>
<td>101</td>
<td>46</td>
<td>55</td>
<td>34</td>
<td>14</td>
<td>20</td>
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<td>Patients with pre-treatment parenthood</td>
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<td>Patients with desire for post-treatment parenthood</td>
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<td>Patients who attempted post-treatment pregnancy</td>
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<td>Patients who achieved post-treatment pregnancy (% of patients attempting)</td>
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<td>Patiens who achieved post-treatment parenthood</td>
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<td>Total number of pregnancies (post treatment)</td>
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<td>Deliberate abortion</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<td>Total number of children (post-treatment)</td>
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<td>Interval between completion of treatment and parenthood, months (range)</td>
<td>65.5 (21–165)</td>
<td>60 (21–146)</td>
<td>70 (25–165)</td>
<td>81 (25–165)</td>
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<td>81 (25–165)</td>
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<td>Childless patients (% of all patients)</td>
<td>33 (32.7)</td>
<td>10 (21.7)</td>
<td>23 (41.8)</td>
<td>11 (32.4)</td>
<td>5 (35.7)</td>
<td>6 (30)</td>
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</table>

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone.
one-fifth of surviving patients refraining from post-treatment parenthood because of a personal decision. The average number of children in female study patients (1.37) was similar to the cohort-specific fertility rates in the female general population, ranging from 1/654 in the 1955 birth cohort to 1/454 in the 1970 birth cohort, the latter by age 40 years (Human Fertility Database, Max Planck Institute for Demographic Research, Germany, and Vienna Institute of Demography, Austria, available at www.humanfertility.org, data downloaded 24 March, 2013). Age at the birth of first child did not differ between female patients in our cohort and the general female population (log-rank test, \( P = 0.172 \), Fig 1) whereas the birth of first child was significantly delayed in male study patients versus the male general population (\( P = 0.00148 \)).

In summary, our data unequivocally confirm the postulated low risk of infertility after treatment with CHOP chemotherapy. To the best of our knowledge, we show for the first time that CHOP plus etoposide or dose-dense CHOP-like regimens are also associated with a low risk of infertility. Despite these favourable results on the fertility effects of CHOP and CHOEP, as pointed out by Greaves et al (2013), all lymphoma patients of reproductive age should be offered counselling with regard to the impact of the intended treatment on fertility and family planning.

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Competing interests

The authors have no competing interests.

Author contributions

JM designed the study, collected, analysed and interpreted the data and wrote the manuscript, DT analysed and interpreted the data and critically revised the manuscript, SD, TS, MZ, and EK analysed the data and critically revised the manuscript, TR collected the data and critically revised the manuscript, MW-H, MP, and ADH designed the study and critically revised the manuscript. JM, DT, SD, TS, MZ, EK, MW-H, MP, and ADH approved the submitted and final version of the manuscript.

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References


