SHORT COMMUNICATION

Fertility and ovarian function are preserved in women treated with an intensified regimen of cyclophosphamide, adriamycin, vincristine and prednisone (Mega-CHOP) for non-Hodgkin lymphoma

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BACKGROUND: Intensive chemotherapy is widely used to improve the outcome of aggressive non-Hodgkin lymphoma (NHL). Since these regimens may cause premature ovarian failure (POF), the ovarian function was studied in 13 consecutive women aged ≤ 40 years, treated with four cycles of intensified CHOP (cyclophosphamide 2000–3000 mg/m² per cycle doxorubicin 50 mg/m², vincristine 1.4 mg/m² (maximum 2 mg) and prednisone 100 mg/day were given every 3 weeks). METHODS: Patients aged < 60 years with aggressive NHL were eligible for participating in a non-randomized phase II study if they had stage I, II, B, bulky, or stages III, IV disease with the age-adjusted international prognostic index of low–intermediate to high-risk score. Seven patients were concomitantly treated with d-TRP6-GnRH analogue (Decapeptyl; Ferring, Germany) for minimizing gonadal toxicity. RESULTS: With a median follow-up of 70 months only one patient had POF, while 12 patients retained fertility and eight conceived spontaneously delivering 12 healthy babies. CONCLUSION: It appears that high-dose cyclophosphamide does not affect the ovarian function or fertility in patients exposed to this medication during four consecutive cycles of intensified CHOP.

Key words: fertility/GnRH analogue/lymphoma/post-chemotherapy

Introduction

The standard treatment of aggressive non-Hodgkin lymphoma (NHL) includes cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (maximum 2 mg) and prednisone 100 mg/day for 5 days (CHOP). However, since the delineation of clearly defined prognostic factors, a more intensive approach has been considered appropriate in patients with intermediate–high and high-risk disease (Shipp et al., 1995). Various treatment regimens were proposed, including induction followed by intensive therapies or up-front autologous bone marrow transplantation (Milpied et al., 2004). Although a more aggressive therapy may result in an improved remission rate, it is usually associated with amenorrhea and infertility in 33–75% of patients (Muller and Stahel, 1993; Sanders et al., 1996; Gulati and Van Poznak, 1998). The use of a GnRH analogue may help to preserve fertility in some female patients exposed to conventional dose chemotherapy (Pereyra Pacheco et al., 2001; Blumenfeld et al., 2002); however, its efficiency may be limited in patients undergoing high-dose chemotherapy with stem cell rescue.

Materials and methods

Patients aged < 60 years old with aggressive NHL were eligible for non-randomized phase II study if they had stage I, II, B, bulky, or stage III–IV disease with the age-adjusted international prognostic index of low–intermediate to high-risk score. Patients were exposed to four cycles of high-dose cyclophosphamide given in a phase II study. At the beginning of the study, patients were given 2000 mg/m² dose divided for 2 days, and later on, when no side-effects were reported, the cyclophosphamide dose was increased to the current dose of 3000 mg/m² dose divided for 2 days. Of these patients, 10 received the regimen containing cyclophosphamide 3000 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (2 mg maximum) and prednisone 100 mg/day for 5 days, one was given cyclophosphamide 2500 mg/m² and in two other patients the cyclophosphamide dose was decreased to 2000 mg/m². In all the patients this course was followed by G-CSF 5 μg/kg starting on day 4 from the beginning of chemotherapy until the neutrophil count was > 1500/μL. Patients had 67 gallium or 18F-fluorodeoxyglucose (positron emission tomography) scintigraphy at diagnosis and after one or two cycles of chemotherapy to assess response to therapy. Female patients aged < 40 years were given d-TRP6-GnRH analogue (Decapeptyl C.R.; Ferring Germany) 3.75 mg as an i.m. monthly depot injection upon their consent. Some patients for...
whom urgent therapy was required and others who did not wish to receive GnRH analogue had chemotherapy only. Cyclic ovarian function was defined as the occurrence of regular menses, in the presence of normal gonadotrophin and sex steroids levels, follicles visualized on transvaginal ultrasonography, or pregnancy.

**Results**

From 1996 to 2003, 58 consecutive patients entered this study. The overall complete response rate (CR) was 88% (51/58). At a median follow-up of 30 months (range 6–94 months), the 3 year failure-free survival and overall survival were 63 and 84% respectively. Fifteen patients relapsed. Twenty female patients aged 18–40 (median 27) years were treated as per protocol. Thirteen of those who achieved complete remission (CR) and required no additional chemotherapy were evaluated for their fertility status. Seven patients were also treated with GnRH analogue in parallel with chemotherapy.

With a median follow-up of 70 months (ranging 23–99 months), 12 out of 13 patients (92%) experienced recovery of ovarian function. Eight patients conceived spontaneously, five of them following GnRH analogue co-treatment during the chemotherapy course and 12 healthy babies were delivered. Four women delivered singleton neonates each, another three patients had two successful deliveries each and one patient delivered twins (Table I). One patient, aged 40 years, who did not receive GnRH analogue, experienced premature ovarian failure.

**Discussion**

Young patients with aggressive NHL may benefit from escalated chemotherapy with improved CR and survival (Milpied et al., 2004). Preservation of ovarian function is clearly important; however, ovarian cryopreservation is still at experimental stages and its functional outcome needs further supportive evidence. A successful pregnancy following this technique was recently reported (Donnez et al., 2004).

Chemotherapy protocols including alkylating agents are frequently associated with gonadal toxicity. They may be detrimental even to resting and immature oocytes and possibly damage pre-granulosa cells of primordial follicles (Meirion, 2000). The available data suggest that >90% of females treated with CHOP do preserve ovarian function, possibly due to a relatively low cumulative dose of cyclophosphamide, totaling 4.5 to 6 g/m².

The POF rate was reported to be as high as 60–90% in the application of regimens with higher doses of alkylating agents, used as conditioning for stem cell transplantation (Salooja et al., 2001).

The British Medical Research Council study (MRC AML 10) trial for patients with acute leukaemia revealed that hormonal disorders were more common in autologous or allogeneic bone marrow transplantation, 58 or 78% respectively, compared with 23% in a cohort of patients who had intensive consolidation chemotherapy. The infertility among women post transplantation was 64 versus 12% post intensive consolidation (Watson et al., 1999).

Apparently, POF correlates with age and cumulative dose of the alkylating agent. Time schedule may also play a role. The cumulative cyclophosphamide dose given in the study protocol (8–12 g/m²) is within the range of doses given during stem cell transplantation. Yet, the time schedule and dose intensity are different and the incidence of POF is considerably lower (8 versus 60–90%) in the former protocol. Most patients undergoing high-dose chemotherapy have been exposed to a primary regimen followed by salvage regimen. They acquired cumulative gonadal damage, which makes it hard to compare their results with those of the patients receiving the first line protocol. The use of GnRH analogue in combination with chemotherapy may possibly have a protective effect on oocytes (Blumenfeld et al., 2002). However, this has been demonstrated by a few centres in non-randomized studies (Fox et al., 2001; Pereyra-Pacheco et al., 2001; Recchia et al., 2002). These results await confirmation and mechanisms need to be elucidated. Its impact is likely to be dependent on patients’ age, chemotherapeutic agents used, cumulative doses of chemotherapy, and schedule. Although

![Table I. Patient characteristics, therapy and fertility status](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Histology</th>
<th>Stage</th>
<th>Cumulative cyclophosphamide (mg/m²)</th>
<th>GnRH analogue</th>
<th>Follow-up (months)</th>
<th>Ovarian function *fertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>DLC</td>
<td>II B bulky</td>
<td>8000</td>
<td>No</td>
<td>99</td>
<td>Del. after 24m, 50m</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>DLC</td>
<td>I A bulky</td>
<td>8000</td>
<td>No</td>
<td>98</td>
<td>COF</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>DLC</td>
<td>III A bulky</td>
<td>12000</td>
<td>No</td>
<td>94</td>
<td>COF</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>DLC</td>
<td>IV A bulky</td>
<td>11500</td>
<td>Yes</td>
<td>95</td>
<td>Del after 37m, 94m</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>ANAP LC</td>
<td>III B non-bulky</td>
<td>10580</td>
<td>Yes</td>
<td>74</td>
<td>Del. after 26m twins</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>DLC</td>
<td>IV B bulky</td>
<td>12000</td>
<td>Yes</td>
<td>70</td>
<td>COF</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>DLC</td>
<td>II A bulky</td>
<td>11250</td>
<td>No</td>
<td>74</td>
<td>Del. After 54m</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>Angiocentric B-cell</td>
<td>I A non-bulky</td>
<td>12000</td>
<td>Yes</td>
<td>67</td>
<td>Del. After 35m</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>DLC</td>
<td>II B bulky</td>
<td>12000</td>
<td>Yes</td>
<td>58</td>
<td>Del after 48m</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>DLC</td>
<td>III B bulky</td>
<td>12000</td>
<td>No</td>
<td>61</td>
<td>Del. after 25m</td>
</tr>
<tr>
<td>11</td>
<td>30</td>
<td>DLC + sclerosis</td>
<td>II B non-bulky</td>
<td>12000</td>
<td>Yes</td>
<td>62</td>
<td>Del. after 26m, 45m</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>DLC</td>
<td>IV A bulky</td>
<td>12000</td>
<td>No</td>
<td>23</td>
<td>POF</td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>DLC</td>
<td>II A</td>
<td>12000</td>
<td>Yes</td>
<td>23</td>
<td>COF</td>
</tr>
</tbody>
</table>

DLC = NHL diffuse large B-cell lymphoma; COF = cyclic ovarian function; ANAP LC = anaplastic large cell lymphoma; Angiocentric = angiocentric B-cell lymphoma; Del = delivery; DLC + sclerosis = diffuse large cell lymphoma of mediastinum with sclerosis; POF = premature ovarian failure.

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the study protocol causes only a minimal impairment to the reproductive function, seven out of 13 patients were also treated with GnRH analogue. There was no significant difference whether GnRH analogue was given in respect to subsequent cyclic menses or fertility. Obviously, a larger cohort of patients is needed to determine the possible additional beneficial role of GnRH analogue co-treatment in this protocol.

In conclusion, this report suggests that increasing the dose of cyclophosphamide only, administered during a short period of time, may be an alternative option in the treatment of aggressive NHL, resulting in a minimal rate of gonadal toxicity. The preliminary result of 92% of patients retaining cyclic ovarian function with this protocol awaits validation in a larger series.

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References

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