Low dose intravenous cyclophosphamide–induced ovarian failure in Chinese patients with lupus nephritis

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Objective: The efficacy of cyclophosphamide (CYC) in the treatment of lupus nephritis has been well documented. However, few studies regarding its effects on ovarian function in Chinese lupus patients have been reported.

Method: One hundred and six lupus nephritis patients treated with CYC, the effects of the starting age of CYC treatment, total doses of CYC administration and routes of administration on ovarian failure were investigated.

Results: The mean cumulative dose of CYC was less than 4.5 gm in all patients. By logistic regression, we found that ovarian failure was significantly correlated with starting age of intravenous CYC treatment. None of the patients that started intravenous CYC therapy before the age of 25 had ovarian failure while 15.7% of those starting CYC treatment between the ages of 26 to 44 developed permanent amenorrhea and all patients receiving CYC after the age of 45 developed ovarian failure (p<0.0001). Patients taking oral CYC had a higher frequency of developing permanent amenorrhea compared with an intravenous route (p=0.024).

Conclusion: We conclude that younger patients had a decreased risk of developing CYC-induced ovarian failure. Monthly intravenous administration has less ovarian toxicity than a daily oral regimen.

Key words: Lupus nephritis, cyclophosphamide, ovarian failure, Chinese lupus patients

Introduction

Cyclophosphamide (CYC) is widely used in renal and major extra-renal manifestations of systemic lupus erythematosus [1-7]. Although mycophenolate mefetil (MMF), a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) have been proven for efficacy in severe lupus nephritis, CYC remains the standard treatment for lupus nephritis [8-11]. Complications of CYC include hemorrhagic cystitis, gonadal toxicity, bone marrow suppression, infection and malignancies [12,13]. Bladder complications can be reduced by adequate hydration and risk of infection can be controlled by careful evaluation before administration of CYC. However, because the majority of lupus patients are women of child-bearing age, ovarian toxicity is an important concern before the use of CYC therapy in premenopausal women. Furthermore, premature ovarian failure increases risk of osteoporosis, artherosclerosis, myocardial infarction and stroke. Several studies have shown CYC-induced gonadal toxicity in patients with malignant disease or hematological disorders [14-16], but dose and treatment schedules differ from what we usually use in lupus patients. To our knowledge no more than three papers regarding the effect of CYC on fertility in Chinese lupus patients have been documented [17-19].

In the present study, we evaluated the risk of permanent amenorrhea in Chinese female lupus patients treated with low dose CYC and find that younger
patients have less risk of developing CYC-induced ovarian failure.

**Materials and Methods**

All women with lupus nephritis who had been treated with CYC in our Lupus Clinic from 1983 to 1993 were reviewed retrospectively. Detail records on dose, route and duration of CYC treatment were reviewed. Patients with regular menstruation before CYC therapy were considered eligible for this study. Those who had abnormal menstrual problems before CYC therapy or aged older than 50 years-old were also excluded.

A detailed interview regarding menstrual history was administered by a trained nurse or doctor in person or by telephone. Menstrual condition was documented in the visit notes.

Transient amenorrhea is defined as lack of menstruation for at least 3 months after CYC therapy and then regaining of normal menstrual cycle later. Permanent amenorrhea is defined as amenorrhea for more than one year after cessation of CYC therapy, and is considered to be ovarian failure.

The data was analyzed with SPSS program, Version 10.0 (SPSS Inc, Chicago, IL, USA) for Windows. Logistic regression was used to study the factors associated with development of CYC-induced sustained amenorrhea. Chi-squared test were used to compared 1) the starting age of CYC therapy; 2) the total dose of CYC; 3) the duration of CYC therapy; and 4) the route of administration.

Statistical significance was defined as a p value <0.05.

**Results**

One hundred and six women were enrolled in this study. The mean age was 29.03 years old (range from 14 to 47).

Patients were divided into three groups according to starting age of CYC therapy: group I (n = 41) contained those younger than 25 years old; group II (n = 60) contained those aged between 26 to 44 and group III (n = 5) contained those older than 45 years. Most patients received monthly CYC for six to twelve consecutive months. The mean duration of CYC therapy in group I was 8.7 months, 8.9 months in group II and 6.8 months in group III. The mean total dose of CYC was 4353 mg in group I, 4462 mg in group II and 3400 mg in group III patients (p=0.65). All patients in group I received intravenous CYC, 51 out of sixty patients in group II received intravenous CYC, 9 received oral CYC and all five patients in group III received intravenous treatment.

Only two patients (4.9%) in group I developed transient amenorrhea but resumed their normal periods after cessation of CYC therapy. None (0%) developed permanent amenorrhea in group I. Eight out of fifty-one patients (15.7%) in group II patients that received intravenous CYC developed permanent amenorrhea, nine (17.6%) developed transient amenorrhea. All patients in group III (100%) developed ovarian failure after CYC therapy (p<0.0001). Five out of nine (55.6%) group II patients that received oral CYC developed permanent amenorrhea (p=0.024 vs. IV CYC). (Table 1 and Figure 1)

This reflected the fact that the age of beginning CYC therapy was the critical factor in the development of ovarian failure. Patients taking oral CYC had a higher risk of developing ovarian failure than via intravenous

**Table 1. Number of patients developed amenorrhea after cyclophosphamide therapy**

<table>
<thead>
<tr>
<th>Age of beginning CYC</th>
<th>Route</th>
<th>No of patient</th>
<th>Transient amenorrhea</th>
<th>Permanent amenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤25 y/o</td>
<td>IV</td>
<td>41</td>
<td>2 (4.9%)</td>
<td>0</td>
</tr>
<tr>
<td>26-44 y/o</td>
<td>IV</td>
<td>51</td>
<td>9 (17.6%)</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td>≥45 y/o</td>
<td>PO</td>
<td>9</td>
<td>0</td>
<td>5 (55.6%)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>5</td>
<td>0</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

*p value*  

Abbreviations: CYC = cyclophosphamide, No = number, IV = intravenous, PO = oral
administration. There was no correlation between total cumulative dose and the duration of therapy and the development of ovarian failure in our study.

**Discussion**

Our data suggests that CYC-induced ovarian failure is age-dependent, and younger patients have a decreased risk of developing ovarian failure. Sanders et al. [20] measured luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in females treated with CYC for aplastic anemia and leukemia and found that all patients under 25 years of age at the time of treatment had normal gonadotrophin levels, but two-thirds of the patients aged more than 25 years had elevated LH and FSH. Balow et al. [21] reported that in patients treated with CYC for lupus nephritis, ovarian failure in 100% of those greater than 30 years of age, in approximately 50% between 20-30 years and in 13% of patients less than 20 years of age. Bogdanovic et al. [22] evaluated 12 women who were treated with CYC for childhood nephrotic syndrome before or during puberty. They found that all patients had normal pubertal development and a regular menstrual pattern. Our study confirmed that CYC given in a relatively small doses to women younger than 25 year old is safe, while females receiving CYC aged 46-50 years, had the highest risk of developing ovarian failure.

Whether these patients who maintained normal menstrual cycles will have premature ovarian failure or not years later is unknown. As CYC may accelerate the loss of follicles that naturally occurs with aging, it is possible that it may cause menopause earlier than expected in some patients.

Some authors report exposure to doses greater than 18 g, even in females younger than 20 years, can cause gonadal toxicity [23]. There have been studies in patients with systemic lupus erythematosus receiving intermittent pulse CYC therapy which showed that sustained amenorrhea is related to both age and dose of CYC [24]. Martin-Suarez et al. reported in 1997 that none of his patients with severe connective tissue disease receiving low dose CYC therapy (cumulative dose <2.5 gm) developed ovarian failure [25]. However, in the present study, sustained amenorrhea is related to the age but not to the cumulative dose. A possible reason is because the cumulative dose in our patients was much smaller than the critical dose (18 g). Boumpas et al. [26] published a paper in 1992 showing that patients receiving long-courses of intravenous CYC (monthly for six months and then every three months for at least two additional years) had a better renal outcome. The patients we enrolled from 1982 to 1993 and received a relatively short-course of CYC pulse therapy compared with standard long-course regimen. This explains why the cumulative dose in our study is much smaller than the standard long-course CYC regiment.

Premature ovarian failure is not only a problem of fertility, but also causes in the acceleration of arteriosclerosis and osteoporosis. Patients with systemic lupus erythematosus have a longer life expectancy than before; hence premature ovarian failure is becoming an issue. Careful evaluation and information about potential ovarian toxicity before the administration of CYC in lupus patients older than 25 years old is crucial.

The number of germ cells is limited, fixed since fetal life, and gradually declines with age [27]. The mechanism of ovarian toxicity caused by CYC has been studied in animal models [28,29]. The pooling of growing follicles appear to be more vulnerable to cytotoxic effects than resting small follicles [30]. CYC destroys the developing follicles by attacking dividing granulosa cells, reducing their steroid secretion, and leading to an increase in pituitary gonadotrophin release, which enhances further recruitment of follicles into the pool of maturing follicles that are more susceptible to CYC toxicity. These events result in accelerated depletion of ovarian follicles.

Somers et al. recently reported that treatment with

### References

Table 2. Strategies for preservation of fertility and ovarian function in cyclophosphamide-treated lupus patients

<table>
<thead>
<tr>
<th>Strategy</th>
<th>References</th>
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<tbody>
<tr>
<td>Administration of the small effective dose of cyclophosphamide</td>
<td>Raptopoulou et al. [33]</td>
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<tr>
<td>Consideration of alternative therapies to cyclophosphamide</td>
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<tr>
<td>Reduction in cumulative drug dose by the use of azathioprine or mycophenolate</td>
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<tr>
<td>Administration gonadotoxic drugs during menstruation</td>
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<tr>
<td>GnRH-a cotreatment (Lupron®)</td>
<td>Ghosh et al. [34]</td>
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<tr>
<td>Cryopreservation of mature metaphase II oocytes</td>
<td>Donnez et al. [35] Wright et al. [36]</td>
</tr>
<tr>
<td>Cryopreservation of embryos</td>
<td>Posada et al. [37] Lobo, R.A. [38]</td>
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a gonadotrophin-releasing hormone analog (GnRH-a, Lupron®) during CYC therapy significantly reduces the risk of premature ovarian failure in woman with severe lupus [31]. The protective effects may be related to the inhibition of ovarian mitotic activity by stimulating the secretion of gonadotrophins luteinizing hormone and follicle stimulating hormone [32,33]. The strategies for preservation of fertility and ovarian function in CYC-treated lupus patients are summarized in the Table 2 [33-38].

In conclusion, our study revealed that CYC-induced ovarian failure in Chinese patients with lupus nephritis is significantly related to the beginning age of therapy. Monthly intravenous administration causes less ovarian toxicity than a daily oral regimen. Clinicians must use different strategies to preserve ovarian function in CYC-treated lupus patients to ensure a better quality of life for lupus patients.

References

在有狼瘡性腎炎的華人因低劑量環磷醯胺治療引起的卵巢功能衰竭

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前言：環磷醯胺在治療狼瘡性腎炎的效果已經是證據充分的。然而只有少數研究探討其在狼瘡性腎炎的華人病患對卵巢功能的影響。方法：106名狼瘡性腎炎的病患接受環磷醯胺治療，我們研究病患接受環磷醯胺治療的起始年紀、環磷醯胺服用的總劑量及使用途徑對於卵巢功能衰竭的影響。結果：在所有病患，環磷醯胺的平均累積劑量少於4.5克。藉由統計回歸法我們發現卵巢功能衰竭與環磷醯胺治療的起始年紀有統計學上的意義。沒有任何小於25歲的病患在開始靜脈注射環磷醯胺治療後有卵巢功能衰竭的情形；介於26-44歲之間的患者有15.7%會發展成永久性的卵巢功能衰竭，且在所有年齡大於45歲的患者接受靜脈注射環磷醯胺治療後會導致卵巢功能衰竭(p<0.0001)。接受口服環磷醯胺治療之病患比靜脈治療病患易引起卵巢功能衰竭(p=0.024)。結論：我們的研究顯示年輕的患者對環磷醯胺治療引起的卵巢功能衰竭危險性較小。每月靜脈注射給予亦較每日口服給藥對卵巢影響較小。

關鍵詞：狼瘡性腎炎、環磷醯胺、卵巢功能衰竭、華人狼瘡病患