Ovarian Insufficiency is Major Short-term Toxicity in Systemic Lupus Erythematosus Patients Treated with Cyclophosphamide

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Abstract

Objective: To study the toxicities associated with pulse cyclophosphamide therapy and to compare them with patients without cyclophosphamide exposure.

Methods: In this retrospective cross-sectional observational study Systemic Lupus Erythematosus (SLE) patients who had received immunosuppressive agents in the past were interviewed in the Out Patient Department for drug related toxicities. Patients were asked about any history of tuberculosis, herpes zoster, hemorrhagic cystitis or ovarian toxicity in the past.

Results: Among 90 patients 84 (93%) were females. The mean age at the start of therapy was 29.7 ± 9.95 (range 8-67) years. Thirty-eight patients (34 females) had received cyclophosphamide. The mean cumulative dose of cyclophosphamide was 9.2± 4.2 (range 1-20) grams and mean time duration from start of cyclophosphamide exposure to enrollment was 3.6 ± 3.2 (range 0.4- 11) years. Of the rest 52 (50 females) patients 30 had received only steroids, 18 had received only azathioprine, and 4 patients had received only hydroxychloroquin. There was a higher occurrence of transient amenorrhea (10/34 versus 2/50, p<0.001) and premature menopause (6/34 versus 1/50 p<0.02) in patients treated with cyclophosphamide as compared to those who had not received it. Patients with cyclophosphamide exposure had higher prevalence of Hematuria (2 versus 0 patients), tuberculosis (4 versus 1 patient) and herpes zoster infection (3 versus 0 patients) but these differences were not significant statistically.

Conclusions: Transient amenorhea was seen in one-third and premature menopause was seen in one-sixth of SLE with cyclophosphamide exposure.

Editorial Viewpoint

- Transient ammonerhea and premature menopause were predominant toxicities in SLE patients treated with pulse cyclophosphamide.
- Occurrence of other toxicities like hematuria, tuberculosis and herpes zoster infections were not significant.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder, which may affect any organ. The clinical manifestations may range from malar rash to life threatening renal and central nervous system (CNS) involvement. In recent years the mortality of SLE has decreased due to use of immunosuppressive drugs.  

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Received: 06.11.2014; Revised: 07.01.2015; Re-revised: 16.03.2015; Accepted: 24.03.2015
Table 1: Clinical features of the patients at presentation (n=90)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>76</td>
</tr>
<tr>
<td>Arthritis</td>
<td>68</td>
</tr>
<tr>
<td>Malar rash</td>
<td>52</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>47</td>
</tr>
<tr>
<td>Nephritis</td>
<td>45</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>39</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>18</td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>16</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>13</td>
</tr>
<tr>
<td>Alopeica</td>
<td>10</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>9</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2: Complications of Immunosuppressive therapy (n=90)

<table>
<thead>
<tr>
<th>Complications</th>
<th>Cyclophosphamide exposure (n=38) Females (34)</th>
<th>No Cyclophosphamide exposure (n=52) Females (50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian insufficiency</td>
<td>10</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premature menopause</td>
<td>6</td>
<td>1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant

patients, neuropsychiatric lupus four patients, myocarditis and autoimmune hemolytic anemia one patient each.

Patients were included in the study after informed consent. Ethics committee permission was not required as this was observational study. Patients with chronic renal failure were excluded from the study. Demographic data of the patients was recorded. Data about duration as well as the cumulative doses of the immunosuppressive drugs was obtained from the treatment records. Cumulative doses of the drugs were calculated by summing up all the doses in the treatment records.

Ovarian toxicity was defined as occurrence of transient amenorrhea or premature menopause occurring after institution of therapy for SLE. Transient amenorrhea was defined as amenorrhea lasting more than 4 months in the absence of pregnancy and premature menopause was defined as amenorrhea lasting more than 12 months before the age of 45 years. Patients who were postmenopausal or had secondary amenorrhea (hysterectomy, oophrectomy, pelvic irradiation) were excluded. Data was also collected about any history of tuberculosis or intake of anti tubercular treatment after exposure to immunosuppressive drugs. Hemorrhagic cystitis was diagnosed if patients had history of gross hematuria in the past. Herpes zoster infection was diagnosed if patient reported painful dermatomal vesicular eruptions.

Patients were divided into two groups, i.e. those who had received CYC and the rest of the patients who had received corticosteroids, AZA or hydroxychloroquin. The data was analyzed using SPSS 13, Chi square test was used to compare the difference in complications between the two groups, and p value of less than 0.05 was considered statistically significant.

Results

A total of 90 patients were enrolled in the study out of which 84 (93%) were females. The mean age at the start of therapy was 29.7 ± 9.95 (range 8-67) years. Fever, malar rash, and arthritis were the most common presenting complains (Table 1). Thirty-eight patients (34 females) had received CYC.

The mean cumulative dose of CYC was 9.2 ± 4.2 (range 1-20) grams and mean time duration from start of CYC exposure to enrollment was 3.6 ± 3.2 (range 0.4-11) years. Of the rest 52 patients (50 females), 30 had received only steroids, 18 had received azathioprine, and 4 patients had received only hydroxychloroquin. A total of 12 patients developed ovarian insufficiency and 7 patients developed premature menopause. Patients with CYC exposure had significantly higher incidence of ovarian insufficiency (26% vs. 4%) or premature menopause (15% vs. 0.5%) as compared to patients who did not receive CYC (Table 2). Overall 42% of CYC treated patients had ovarian toxicity i.e. either ovarian insufficiency or premature menopause.

Patients with CYC exposure had higher chance of getting Tuberculosis, Hematuria or Herpes
Zoster though the difference was not statistically significant (Table 2).

**Discussion**

Cyclophosphamide is a potent immunosuppressive agent and a useful drug in the treatment of severe lupus especially lupus nephritis and CNS lupus. Though CYC has changed the way the severe lupus is managed it has not been without attendant side effects.

Premature menopause is always a serious concern when treating young females with SLE who are in the reproductive age group. The premature menopause resulting in the withdrawal of estrogen leads to premature osteoporosis and higher risk of atherosclerosis and cardiovascular mortality.

Only six (17%) patients treated with CYC in our study developed premature menopause which is low as compared to some of the studies reported from the other parts of the world which have reported incidence to be as high as 54% (Table 3). The difference could be due to the higher cumulative doses and use of oral CYC therapy in the past as well as younger age of our patients in our study. In a study premature menopause was related to both the age at CYC therapy and number of doses of CYC. Ovarian insufficiency occurred in ten (29%) patients treated with CYC which again is lower than figures reported in the western literature. The reasons for the difference could be same as that have been discussed for premature ovarian failure. Only one patient in the group not exposed to CYC developed premature menopause suggesting that the premature menopause in the CYC treated group was due to the cytotoxic effect of CYC and not due to SLE itself.

The mechanism of CYC induced ovarian toxicity has been studied in animal models. In mice intraperitoneal injections of CYC decreases the number and size of the follicles. Growing follicles are more prone to the CYC induced damage leading to decrease in estrogen levels which by feedback mechanism leads to increase in the follicle stimulating hormone (FSH) levels. This increase in FSH levels accelerates the development of primordial follicles exposing them to CYC and follicular destruction continues. Also with the increase in age the number of ovarian follicles goes on decreasing. The reserve of ovarian follicles appears to be an important predictor of premature menopause in CYC treated patients with various studies showing increasing risk of premature menopause with higher age at CYC exposure. Strategies have been suggested to decrease the risk of ovarian toxicity caused by CYC exposure. Oral contraceptives and gonadotropin releasing hormone analogs suppress the levels of FSH and leutinising hormone (LH) decreasing the follicular maturation and resultant CYC toxicity but synthetic steroids are known to increase the flares of SLE and could lead to increase in thrombotic events in SLE patients with antiphospholipid antibodies.

Newer regimens of short courses of pulse CYC for six months followed by azathioprine have shown to be promising in controlling the disease activity and may also help in reducing the CYC exposure and preventing ovarian toxicity. Mycophenolate Mophetil in recent studies has shown to be comparable to pulse CYC in controlling the disease activity without increasing the risk of ovarian toxicity. Recent reports suggest favorable role of Rituximab in lupus nephritis.

Infection is an an important cause of mortality and morbidity in SLE patients. Though in patients with SLE the presence of disease activity and active renal involvement has been linked to increased risk of infection but studies have shown that inclusion of CYC in the treatment regimen increases the risk of infections. In a recent study where patients suffering from systemic autoimmune diseases and treated with varying doses of cyclophosphamide were studied, infections occurred in 44/168 patients (26.2%). Surprisingly premature menopause occurred only in 5/92 (5.4%) of patients even though the patients received a median cumulative CYC dose of 34.5 grams (range 6–40) at a median age of 39 years (range 34–50). The reason for such a low figure could be that there were only 25 female patients of SLE in this study out of a total group of 92 patients. SLE itself may be a factor in the initiation of premature menopause by autoimmune process which gets augmented by CYC therapy. Other reasons could be the genetic difference which may alter the metabolism of CYC by cytochrome P450 enzymes leading to differential ovarian toxicity in different populations.

In our study we found an increased risk of tuberculosis and herpes in patients treated with CYC though the difference was not statistically significant. This could have been due to small number of events. A recent study
from Argentina found that the cumulative dose of corticosteroid was the only significant risk factor for infection and use of lower doses of steroids with CYC may have an acceptable safety profile.

Hematuria in two patients reflects the bladder injury that CYC can cause by its metabolite acrolein that is excreted in the urine. Sodium 2-mercaptoethanesulfonate (MESNA) can inactivate acrolein and decrease the risk of hemorrhagic cystitis.

Our study is limited by the fact that the levels of follicle stimulating hormone (FSH) and luteinizing hormones (LH) were not done to document premature menopause.

Thus in our study which to our knowledge is first to look for cyclophosphamide toxicity in Indian patients, we found out that ovarian insufficiency is the most common toxicity seen in one-fourth of patients treated with pulse CYC. Premature menopause was seen in one-sixth of the patients treated with CYC. This should be kept in mind when treating young SLE patients in the reproductive age group.

References


