Evidence-based Rheumatology

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Cyclophosphamide therapy induces ovarian failure in premenopausal women affected by systemic lupus erythematosus

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Title: Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy
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Aim: Cyclophosphamide (CYC) is the drug of choice for the treatment of the severe manifestations of systemic lupus erythematosus (SLE). Among the numerous side effects of CYC, ovarian failure is one of the major concerns in premenopausal women. This study was undertaken to determine the incidence of ovarian failure after CYC therapy for SLE, and to identify the risk factors for such a complication.
Methods: The records of 274 female SLE patients (pts) were reviewed retrospectively (years 1971-1997). Pts under 45 years treated with CYC were included for analysis, while pts in whom menopause had occurred before CYC treatment or who had known causes for secondary amenorrhea, with renal impairment or uremia, with previous hormonal treatment were excluded. Two control groups of SLE pts were included for the comparisons: one group under 45 years who had received azathioprine (AZA), but never CYC, and another group of pts under 45 years who had been given either no treatment or hydroxychloroquine, but who had never received AZA or CYC. For both control groups the exclusion criteria were the same as for the CYC group.
For all pts amenorrhea (lack of menses for 4 months), sustained amenorrhea (lack of menses for 12 months) and ovarian failure documented by levels of FSH, LH and estradiol were evaluated. Demographic data, age at SLE onset, disease duration, the autoantibody profile, and clinical features were also recorded. For pts who had received CYC, the age at CYC initiation, the route and duration of CYC, the cumulative dose received, and the mean daily CYC dosage were recorded. Pts who developed amenorrhea after CYC treatment were identified.
Two different CYC regimens were considered in the analysis. In the intermittent intravenous schedule a pulse CYC (0.5-1 g/m^2) was given for 6 months, followed by a pulse once every month for 18 months. In the oral CYC regimen a dose of 1-2 mg/kg/die was given for 6-9 months, and then substituted with AZA. High dose corticosteroid (prednisolone 1 mg/kg/die, subsequently tapered) was administered concomitantly in the CYC-treated pts.
Student's T test for independent samples was used to compare the parametric data between the CYC treated pts who developed ovarian failure and those who did not. Analysis of variance was used to compare the means among multiple groups. The chi-square test was used to study the relationship between the incidence of ovarian failure and increasing age and the cumulative dose of CYC. Risk factors for CYC-induced ovarian failure were studied by multiple logistic regression.
Results: The records of 274 SLE female pts were reviewed: 19 were excluded (age > 45 years, concomitant hormone therapy). Among the 83 CYC-treated pts, 13 were excluded from the analysis due to renal impairment,previous hysterectomy, or previous pelvic irradiation. A total of 70 pts were studied: 54 had received continuous oral CYC and 16 intermittent intravenous therapy. The two control groups consisted of 84 pts treated with AZA who had never received CYC, and 88 pts who had received hydroxychloroquine or no therapy.
In the CYC group a significantly longer SLE duration and a higher frequency of renal and central nervous system involvement were found: these reflect the fact that the CYC-treated pts had more serious disease.
21 CYC-treated pts developed amenorrhea; 18 of these had sustained amenorrhea and documented ovarian failure (overall incidence rate 26%). Only 1 pt in the AZA group (1%) and no pt in the hydroxocloroquine group suffered this complication. The mean time interval between CYC treatment and the onset of amenorrhea in the ovarian failure group was 4.4 months (range 1-12 months). The incidence of ovarian failure showed a linear trend, increasing with increasing age at the start of CYC ($P = 0.007$). The cumulative CYC dose was significantly higher in pts with ovarian failure than in those without (28.3 g vs 15.4 g; $P = 0.004$). The risk of ovarian failure also showed a linear trend, increasing with an increasing cumulative CYC dose ($P < 0.001$). The incidence of ovarian failure in pts receiving oral CYC was 30% (16/54), higher than the incidence in those receiving pulse CYC [13% (2/16)], although the difference was not significant ($P = 0.29$), probably due to the small number of pts treated with the pulse regimen.
The patient's age at the time CYC therapy was initiated ($P = 0.001$) and the cumulative dose of CYC received ($P = 0.02$) were shown by multiple logistic regression to be independent risk factors for CYC-induced ovarian failure.
Conclusions: CYC is at the moment the treatment of choice for life-threatening SLE complications, and cannot be easily substituted by other medications. Ovarian failure is a significant problem in female SLE pts treated with CYC, however, particularly those above the age of 40. The age at the start of CYC therapy and the cumulative dose being the most important determinants for the development of this complication, a shorter course and a lower dosage should be carefully considered.

Comment

In this paper Mok et al. provide evidence that cyclophosphamide can cause ovarian failure in patients undergoing such treatment for systemic lupus.

Given the well known prevalence of the disease in woman during the reproductive age, this observation needs to be carefully considered. The risk of ovarian failure appears to depend on both the cumulative dosage of the drug (without any relationship to the administration schedule) and the age of the patients, women closer to the menopausal age being at greater risk. The message conveyed by this study is certainly important; however, in my opinion, it is more difficult to agree with the authors' conclusions. They recommend the use of a shorter course and a lower dosage of cyclophosphamide in older patients. In this respect I believe that all of us administer the shortest possible course and the lowest dosage of cyclophosphamide able to produce clinical remission or significant improvement in seriously ill patients. We all know that many risks are linked to its use and we all are happy when we can avoid them. Recently, monthly injections of gonadotropin-releasing hormone agonistic analogue were shown to preserve ovarian function in systemic lupus patients treated with cyclophosphamide or chlorambucil (1). Despite the side effects of these injections which were, however, only temporary, this appears to me to offer a more positive approach.

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