Lymphoma Risk in Psoriasis

Results of the PUVA Follow-up Study

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Objective: To assess the risk of lymphoma in patients with psoriasis.

Design: Prospective cohort study that spans 30 years and a systematic review of the literature.

Setting: Sixteen university medical centers.

Patients: A total of 1380 patients with psoriasis who were initially treated with psoralen–UV-A (PUVA) from 1975 through 1976 and who underwent periodic interviews and physician examinations irrespective of their use of any treatment.

Main Outcome Measure: Incidence of lymphoma relative to that expected in the general US population (original primary end point of the study).

Results: The incidence of lymphoma in patients who received PUVA and were not exposed to high levels of methotrexate was comparable to that expected in the general population (incidence rate ratio, 0.85; 95% confidence interval, 0.37-1.67) but was elevated among those exposed to high levels of methotrexate (≥36 months) (incidence rate ratio, 4.39; 95% confidence interval, 1.59-12.06).

Conclusion: Unless exposed to high levels of methotrexate, the risk of lymphoma among members of the PUVA Follow-up Study was comparable to that observed in the general population.

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With the advent of new treatments for psoriasis that may increase the risk of lymphoma, determining the innate risk of lymphoma in patients with psoriasis has become important both for clinical decision making and to ensure the robust evaluation of the risks of newer therapies. Most studies suggest that the risk of lymphoma in patients with psoriasis is comparable to that in the general population. However, 3 recent studies suggested an increased risk of lymphoma in persons with psoriasis.

The PUVA [psoralen–UV-A] Follow-up Study provides a unique resource to establish the incidence of lymphoma among persons with moderate to severe psoriasis, both overall and in subgroups defined by their exposures to established treatments for psoriasis. This cohort study of 1380 persons first treated from 1975 through 1976 now includes nearly 30,000 person-years of follow-up of individuals with moderate to severe psoriasis whose major health events and use of treatments for psoriasis have been prospectively documented during a 30-year period. Determining the risk of lymphoma was an original primary end point for the study. Our data suggest that the innate risk of lymphoma among persons with moderate to severe psoriasis is unlikely to differ substantially from that in the general population.

METHODS

THE PUVA FOLLOW-UP STUDY

The PUVA Follow-up Study is a multicenter prospective cohort study. Its methods have been previously detailed. This study was approved by the Committee for Clinical Investigation of the Beth Israel Deaconess Medical Center. From 1975 through 1976, patients who had enrolled in a therapeutic study of PUVA were asked if they wished to be followed up long term to determine the safety and efficiency of PUVA. Of the 1450 patients participating in the clinical trial, 1380 (95%) enrolled in the long-term prospective study. In addition to baseline information collected from 1975 through 1976, during the subsequent 30 years, these patients were interviewed 22 times. Data collection for this study ended in 2005. Any patient who reported a serious health event, such as lymphoma, was asked to provide permission for us to obtain medical records that pertained to this event. In addition, we used the National Death Index to ascertain cause of death among individuals who were lost to follow-up.

The questionnaires administered at entry (1975-1976) and the 22 follow-up interviews...
administered during the subsequent 30 years included structured questions designed to determine exposure to systemic therapies for psoriasis and to PUVA and UV-B. On the basis of these data, for each calendar year we calculated the extent of exposure to methotrexate, UV-B, and PUVA. As in prior analyses, we defined high-dose exposure to methotrexate as 36 or more months of use and high-dose exposure to UV-B as at least 300 treatments.29

STATISTICAL ANALYSIS

We calculated the expected numbers of lymphoma cases based on data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute.21 We used age- and sex-specific rates applicable to each year of follow-up. To calculate the expected number of lymphoma cases for 2003, 2004, and 2005, we used SEER incidence data for 2002, the most recent year available at the time of analysis (June 2005).

We compared the characteristics of cases to other cohort patients still being followed up (and alive) at the mean year at onset of lymphoma. For categorical variables, we used the χ² test to determine statistical significance with Yates correction when appropriate. For continuous variables, we used the t test. We compared observed and expected number of tumors to calculate the incidence rate ratios (IRRs) and used the Poisson distribution to calculate the 95% confidence intervals (CIs). We compared observed and expected numbers of lymphoma cases for the cohort as a whole and for cohort subgroups as defined by demographic and exposure characteristics.

In calculating expected numbers of tumors based on age-, sex-, and year-specific incidence data from SEER, our analyses were standardized for age, sex, and calendar year. Our multivariate models were Poisson regression models and included all exposures and attributes that were related to lymphoma risk with P ≤ .20 in the univariate analyses. We also tested for possible interactions among exposures that were related to lymphoma risk with P ≤ .20 in the univariate analysis using 2-way interaction terms. In addition, we performed analyses for each significantly associated exposure that were stratified according to level of exposure to other factors that were also significantly associated with lymphoma risk in the univariate analysis.

RESULTS

Of the 1380 patients originally enrolled in the study (1975-1976), at the time of the 22nd and final follow-up interviews (2003-2005), we successfully interviewed 526 (83%) of the 636 who were still alive and participating in the study. As detailed in Table 1, the attrition rate, except because of death, was low until after 1995.

In 28,554 person-years of prospective follow-up, we detected 16 persons with lymphoma, of which 14 had non-Hodgkin lymphoma and 2 had Hodgkin disease. We did not include cutaneous T-cell lymphoma. Of the 16 incident lymphomas, 13 were ascertained through our normal follow-up procedures and 3 from our search of the National Death Index database. Compared with our last report, which spanned 1975 through 1996, the incidence of lymphoma was significantly higher from 1997 through 2005 than in prior years (1975-1996) (IRR, 4.38; 95% CI, 1.60-12.06).

Table 2 compares the characteristics of the cases at the time of detection of lymphoma (mean year of detection, 1995) and the 848 other cohort patients still alive and being followed up in 1995. Patients with lymphoma were significantly older. Except for a significantly higher proportion of patients with high-dose exposure to methotrexate but not PUVA or UV-B, those who developed lymphoma and other active cohort members had similar characteristics and exposures.

Table 3 provides the univariate and multivariate analysis results of associations of various patient exposures and attributes with lymphoma risk. The incidence of lymphoma was significantly higher after 1996 compared with that for the cohort from 1975 through 1996 (Table 3) and for those who had used methotrexate for at least 36 months (Table 3). There was an apparent interaction between the follow-up year and level of exposure to methotrexate. Beginning in 1997, persons who had used methotrexate for at least 36 months had a risk of lymphoma that was more than 7 times that of cohort members earlier in the study and with less exposure to methotrexate (IRR, 7.77; 95% CI, 2.83-21.39).

In the univariate analysis, more than 300 UV-B treatments were significantly associated with lymphoma risk, but this association was no longer significant in the multivariate analysis (Table 3). Because UV-B use and methotrexate exposure were associated, we performed an analysis of the relationship between level of UV-B exposure and lymphoma risk limited to patients with less than 3 years of exposure to methotrexate (ie, low-dose exposure). Patients with high-dose exposure to UV-B but lacking high-dose exposure to methotrexate had no increased risk of lymphoma (IRR, 1.02; 95% CI, 0.21-5.04). Level of exposure to PUVA and having had ionizing radiation therapy for psoriasis were not significantly associated with increased lymphoma risk (Tables 2 and 3). After we adjusted for level of exposure to methotrexate, risk of lymphoma in patients with 400 or more PUVA treatments was nearly identical to that of patients with fewer than 200 PUVA treatments (IRR, 1.12; 95% CI, 0.23-5.38). The frequency of exposure to oral reti-

Table 1. Follow-up Status, by Decade, of 1380 Patients Enrolled From 1975 Through 1976

<table>
<thead>
<tr>
<th>Follow-up Cycle†</th>
<th>Followed up</th>
<th>Lost to Follow-up</th>
<th>Withdrawn</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>1192 (86/98)</td>
<td>20 (1/2)</td>
<td>4 (0/0)</td>
<td>167 (12/0)</td>
</tr>
<tr>
<td>1994-1995</td>
<td>84 (61/89)</td>
<td>6 (4/6)</td>
<td>45 (3/5)</td>
<td>427 (31/0)</td>
</tr>
<tr>
<td>2003-2005‡</td>
<td>526 (38/69)</td>
<td>110 (8/17)</td>
<td>127 (8/17)</td>
<td>817 (48/0)</td>
</tr>
</tbody>
</table>

*Percentages are rounded; therefore, totals may not equal 100.
†Follow-up data in that cycle or in subsequent follow-up.
‡Final follow-up cycle.
After nearly 30,000 person-years of prospective study of the PUVA cohort, the risk of lymphoma observed in cohort members who lacked substantial exposures to methotrexate was nearly identical to that in the general population. In persons with high levels of exposure to methotrexate, a significant increase in lymphoma risk was noted. Level of exposure to PUVA was not associated with lymphoma risk. Risk in the cohort was higher in later years, which may reflect either greater exposure to carcinogenic therapies with the passage of time or that only in later years of the study had a sufficiently long period elapsed for the effect of such exposures to be manifested.

In the univariate analysis, high levels of UV-B were significantly associated with lymphoma risk. However, the results of both the multivariate model and a stratified analysis did not demonstrate any significant relationship between UV-B and lymphoma risk. Population-based studies also indicate that sunlight does not appear to be a risk factor for lymphoma. These results suggest that high levels of exposure to UV-B are more likely to be a marker of greater exposure to other agents that increase lymphoma risk than a true risk factor. When patients with exposure to systemic psoriasis therapies are excluded, most other studies of patients with psoriasis found that the risk of lymphoma is not significantly different in patients with psoriasis than in the general population. Particularly noteworthy is the large case-control study of non-Hodgkin lymphoma in women that found the odds of lymphoma among patients with psoriasis to be nearly identical to that among persons without this disease.

Unlike Epstein-Barr virus–related lymphoma, which usually occurs soon after exposure to immunosuppressive treatments and is related to degree of immunosuppression, our data suggest that long-term and even intermittent exposure at more modest doses of some psoriasis therapies may, after many years, increase lymphoma risk. Others have noted that a higher likelihood of greater exposure to treatments used for more severe psoriasis is also associated with increased risk of lymphoma. In a Medicaid population, Margolis et al noted that those with psoriasis who had used systemic therapies had a risk of lymphoma that was almost twice that of Medicaid enrollees with psoriasis who had no record of using these treatments. Paul et al noted that the risk of melanoma was more than 3-fold higher among patients with psoriasis exposed to 2 years of low-dose, often intermittent cyclosporine treatment compared with other cohort members also treated with cyclosporine but for shorter periods. A Finnish study of patients hospitalized for psoriasis an average of 2.5 times during 10 years observed a modest and significant increase in lymphoma risk. However, similarly designed studies in Sweden and Den-

### Table 2. Demographic Characteristics and Treatment Exposures of Lymphoma Cases and Other Cohort Members

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Cohort Members* (N = 864)</th>
<th>Cases† (n = 16)</th>
<th>Other Cohort Members‡ (n = 848)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>59 ± 13</td>
<td>69 ± 11</td>
<td>59 ± 13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>531 (61)</td>
<td>10 (63)</td>
<td>521 (61)</td>
<td>.93</td>
</tr>
<tr>
<td>Female</td>
<td>333 (39)</td>
<td>6 (37)</td>
<td>327 (39)</td>
<td></td>
</tr>
<tr>
<td>Skin type, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>246 (28)</td>
<td>7 (44)</td>
<td>239 (28)</td>
<td>.17</td>
</tr>
<tr>
<td>3-6</td>
<td>618 (72)</td>
<td>9 (56)</td>
<td>609 (72)</td>
<td></td>
</tr>
<tr>
<td>High-dose methotrexate exposure (as of 1995), No. (%)*</td>
<td>190 (22)</td>
<td>8 (50)</td>
<td>182 (21)</td>
<td>.02</td>
</tr>
<tr>
<td>No. of PUVA treatments, mean ± SD</td>
<td>230 ± 198</td>
<td>228 ± 149</td>
<td>230 ± 199</td>
<td>.23</td>
</tr>
<tr>
<td>High-dose UV-B exposure, No. (%)</td>
<td>300 (35)</td>
<td>8 (50)</td>
<td>292 (34)</td>
<td>.20</td>
</tr>
</tbody>
</table>

Abbreviation: PUVA, psoralen–UV-A.
*With lymphoma or follow-up information.
†At time of diagnosis.
‡Follow-up for nearest median year of lymphoma development (1994-1995).

### Table 3. Univariate and Multivariate Estimates of IRR for Lymphoma Among Persons With Psoriasis, Adjusted for Age and Sex, Based on SEER Incidence Rates*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year, 1997-2005</td>
<td>4.38 (1.60-12.06)</td>
<td>2.54 (1.04-6.23)</td>
</tr>
<tr>
<td>Methotrexate use for ≥36 mo</td>
<td>4.39 (1.59-12.06)</td>
<td>2.54 (1.04-6.23)</td>
</tr>
<tr>
<td>High U-VB exposure (&gt;300 treatments)</td>
<td>2.77 (1.04-7.39)</td>
<td>2.54 (1.04-6.23)</td>
</tr>
<tr>
<td>Skin type 1 or 2</td>
<td>1.90 (0.71-5.11)</td>
<td>NA</td>
</tr>
<tr>
<td>PUVA (≥200 treatments)</td>
<td>1.38 (0.52-3.71)</td>
<td>NA</td>
</tr>
<tr>
<td>High tar exposure</td>
<td>0.74 (0.21-2.58)</td>
<td>NA</td>
</tr>
<tr>
<td>X-ray treatment for psoriasis</td>
<td>0.83 (0.28-2.39)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NA, not applicable; PUVA, psoralen–UV-A; SEER, Surveillance Epidemiology and End Results.
*Based on Poisson regression analysis.

noids, cyclosporine, and biologics (all <2.5% of person-years of follow-up) was too low to assess the relationship between these substances and lymphoma.

Patients without high levels of exposure to methotrexate had a lymphoma risk comparable to that based on SEER data (8 observed, 9.40 expected; IRR, 0.85; 95% CI, 0.37-1.67). In contrast, we observed 8 lymphoma cases in those with exposure to high levels of methotrexate (8 observed, 2.14 expected; IRR, 3.74; 95% CI, 1.61-7.36).
mark did not detect any significant increase in lymphoma among persons hospitalized for psoriasis.5,15,19

Within the spectrum of patients with moderate to severe disease, those with more severe psoriasis are more likely to have greater exposure to systemic therapies. Therefore, we cannot exclude the possibility that the association we observed with high levels of exposure to methotrexate reflects a higher innate risk among those with more severe disease rather than risk related to greater exposure to certain psoriasis therapies. Within the spectrum of moderate to severe psoriasis, the lack of a significant relationship between extent of exposure to PUVA and lymphoma risk, as well as the lack of association of UV-B to lymphoma risk, in both multivariate and stratified analyses argues against increased severity of psoriasis.

Our study has both strengths and weaknesses. Among its strengths are its prospective nature, documentation of exposures, long-term follow-up (nearly 30 years), and high follow-up rates. Still, we detected 3 of 16 lymphoma cases through the National Death Index. This illustrates the difficulty of complete ascertainment of fatal outcomes in a prospective study that uses interviews as its primary basis for data collection.

Because of limited exposure to systemic treatments such as cyclosporine and the biologics, our study lacked the power to assess the risk of lymphoma associated with systemic agents other than PUVA and methotrexate. Furthermore, the higher incidence of lymphoma noted since 1996 suggests that there may be a longer latency between causative exposure and the detection of cancer. Clearly, if we are to exclude a substantial increase in risk of lymphoma in association with newer systemic therapies for psoriasis, long-term studies with sufficiently large study groups, including substantial numbers of patients exposed to high doses of the agents of interest, will be required. High long-term participation rates are needed for a robust analysis, a goal not achieved in the industry-sponsored study of cyclosporine.14

Our findings are potentially important for evaluating the results of long-term safety studies of systemic agents, particularly some biologic modifiers that both mechanistically and on the basis of spontaneous reports have been linked to a higher risk of lymphoma.22,24 Our data and those of other studies suggest an elevated incidence of lymphoma in persons with psoriasis receiving methotrexate and cyclosporine.14 However, our data and those of other studies suggest that it is unlikely that persons with moderate to severe psoriasis have a higher innate risk of lymphoma.

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REFERENCES