Pneumocystis jirovecii pneumonia in B-cell lymphoma patients treated with the rituximab-CHOEP-14 regimen

We report six cases of *Pneumocystis jirovecii* pneumonia (PCP) verified by immunofluorescence/polymerase chain reaction of bronchoalveolar fluid among 46 lymphoma patients (13%) who received rituximab-CHOEP-14 at our institution. PCP prophylaxis should be standard management for this group of patients and also considered for patients treated with rituximab-CHOP-14, CHOP-14 or CHOEP-14.

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Pneumocystis jirovecii pneumonia (PCP) is a rare but serious complication observed in lymphoma patients undergoing treatment. Certain agents, such as fludarabine[1] and the monoclonal antibody alemtuzumab,[2] lead to severe suppression of the cellular immune system, predisposing to opportunistic infections including PCP. Co-trimoxazole prophylaxis is used routinely for patients treated with these agents and minimizes the risk of developing PCP.[3,4] Based on the unexpected clinical observation that many of our lymphoma patients who received the rituximab-CHOEP-14 regimen developed PCP infection, we undertook a survey to investigate this further.

All cases of PCP diagnosed among the entire population of lymphoma patients treated at our institution between 2002 and 2006 and verified by immunofluorescence and/or polymerase chain reaction (PCR) of bronchoalveolar lavage (BAL) fluid were collected and studied in detail. The diagnostic criteria and management strategies for PCP remained unchanged during this period. Patients treated for clinically suspected PCP without verification by BAL were not considered as PCP. Our complete database on chemotherapy administration was then used to define the incidence of PCP in patient groups who had received the CHOP-14, CHOEP-14, CHOP-21, CHOEP-21, with or without rituximab during the same time period. None of the patients were human immundeficiency virus positive and they did not receive PCP prophylaxis.

The numbers of lymphoma patients who received different CHOP-based regimens are listed in Table 1. Six cases of PCP were found among the 46 patients who were treated with CHOEP-14 in combination with rituximab. As shown in Table 2, the PCP developed after four to six cycles of this regimen. We did not observe late cases of PCP occurring more than 1 month after treatment. The diagnosis was made by PCR (6/6 patients) and/or IF (4/6 patients) in BAL fluid. Data on peripheral blood T-cell subsets were available for two patients at the time that PCP was diagnosed: one patient had 0.540×10^9/L CD4 cells, 0.517×10^9/L CD8 cells and a CD4/CD8 ratio of 1.1 whereas the other patient had 0.351×10^9/L CD4 cells, 0.212×10^9/L CD8 cells and a a CD4/CD8 ratio of 1.7. The serum concentration of IgG in the same patient was 3.8 g/L and 6.1 g/L, respectively. All patients had pulmonary infiltrates. All six patients recovered completely after treatment with standard doses of intravenous co-trimoxazole.Although PCP was diagnosed less frequently in the groups receiving the other regimens (Table 1), some cases were found, mostly in patients receiving the 2-week schedules. In the rituximab-CHOP-14 group two out of 32 patients (6%) were diagnosed with PCP. Recent advances in the treatment of non-Hodgkin`s B-cell lymphomas include the combination of CHOP-based therapy with the monoclonal antibody, rituximab.[5-7] By using granulocyte colony-stimulating factor support, the interval between cycles can be shortened from 21 to 14 days and younger patients can even tolerate incorporation of etoposide in the CHOP regimen.[8,9] We have found that lymphoma patients receiving CHOEP every 2 weeks in combination with rituximab have a higher incidence of PCP (13%), compared to patients receiving the other chemotherapy regimens. One recent publication[10] in Hematologica reported an incidence of PCP of 6% in a population of 50 patients with diffuse large B-cell lymphoma treated with CHOP-14 and rituximab. In concordance with this, two of the 32 patients (6%) in our study who were treated with this regimen developed PCP. To our knowledge, depletion of B cells caused by rituximab monotherapy does not increase the risk for PCP infections. However, the combination of this antibody with agents that impair the cellular immune system might predispose to this opportunistic infection. We did not find severely reduced blood levels of $CD4^+$ T-lymphocytes or serum IgG in the two patients tested. Steroids mediate a cytostatic effect on lymphocytes, predisposing to PCP. Intensification of CHO(E)P-based regimens by shortening the interval between cycles to 14 days implies that

Table 1. Patients with non-Hodgkin`s B-cell lymphoma receiving treatment with CHO(E)P-based chemotherapy with or without rituximab from 2002-2006 and the number of cases of PCP.

Regimen	*Patients, n.*	*PCP, n. (%)*
CHOEP*-14	25	1 (4)
CHOEP-21	23	0 (0)
CHOP-14	49	2 (4)
CHOP-21	276	0 (0)
CHOEP-14+rituximab	46	6 (13)
CHOEP-21+rituximab	9	0 (0)
CHOP-21+rituximab	141	2 (1)
CHOP-14+rituximab	32	2 (6)

Cyclophosphamide iv 750 mg/m², doxorubicine iv 50 mg/m², vincristine iv 1.4 mg/m² (max 2 mg), etoposide iv 100 mg/m² day 1-3, prednisolone po 100 mg day 1-5.

Table 2. Characteristics of the patients with malignant B-cell lymphoma who developed PCP during treatment with CHOEP-14 and rituximab.

Patient n.	*Age (years)*	*Rituximab-CHOEP-14**	*PCP BAL IF/PCR*	*Lung infiltrates on chest X-ray*
1	30	4 cycles	+/+	+
2	61	6 cycles	+/+	+
3	47	6 cycles	–/+	+
4	47	6 cycles	+/+	+
5	49	5 cycles	+/+	+
6	58	5 cycles	nd**/+	+

**Cycles administered before PCP; **nd: not done. BAL: bronchoalveolar lavage; IF: immunofluorescence; PCR: polymerase chain reaction.*

a higher dose of prednisolone is administered per week. In addition, etoposide added to CHOP has a negative impact on the mucosal barrier and could facilitate invasion of micro-organisms into the lung tissue. The combination of factors listed above might help to explain the high incidence of PCP. Based on the findings presented in this report we recommend that PCP prophylaxis is given during treatment with the rituximab-CHOEP-14 regimen and continued until one month after the last cycle. Prophylaxis should also be considered for patients receiving other CHO(E)P-based regimens every 2 weeks, especially in combination with rituximab.

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