Primary effusion lymphoma (PEL) is an extremely rare, albeit sinister subtype of non-Hodgkin lymphoma (NHL). At present, treatment information on PEL exclusively arrive from the few available single- or multi-center studies with small, selected patient series1–5; the largest, most recent series including 34 patients with PEL from a single center in France diagnosed between 1996 and 2013.3 Although we certainly appreciate those studies, seeing the rarity of PEL, information from a nonselected group of patients at the population level is needed to complement those studies.

Here, we report the outcomes of a nationwide population-based study on treatment and survival among 25 newly diagnosed patients with PEL in the Netherlands.

We identified patients diagnosed with PEL between 2002 and 2015 from the nationwide population-based Netherlands Cancer Registry (NCR) using International Classification of Diseases for Oncology Third Edition morphology code 9678. The NCR has a nationwide coverage of >95% of all newly diagnosed malignancies in the Netherlands. The NCR relies on comprehensive case notification through the Nationwide Network of Histopathology and Cytopathology and the National Registry of Hospital Discharges (ie, outpatient and inpatient discharges). After case notification, trained registrars from the NCR collect information on several patient (eg, date of birth and sex) and tumor characteristics (eg, date of diagnosis and morphology), as well as details on treatment through retrospective medical records review. According to the Central Committee on Research Involving Human Subjects, this noninterventional, retrospective study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved use of anonymous data for this study.

Overall survival (OS) was measured with the Kaplan-Meier method from the date of PEL diagnosis until death or last of follow-up (February 1, 2017), whichever occurred first. Progression-free survival (PFS) was calculated from the start date of first-line chemotherapy to progression or death from any cause, whichever occurred first. Patients who were alive without progression were censored at time of last follow-up. Disease response to antilymphoma therapy was assessed by physician assessment using computed tomography or combined positron emission tomography/computed tomography. All statistical analyses were performed with STATA/SE 14.1 (StataCorp, College Station, TX).

The demographic and clinical characteristics of 25 patients included in this study are presented in Table S1 (Supplemental Digital Content, http://links.lww.com/HS/A16). The median age at diagnosis was 53 years (range, 30–81). The great majority of patients were male (22/25; 88%) and HIV positive (19/25; 76%). HIV-positive patients were younger at PEL diagnosis than HIV-negative patients (median age 49 vs 70 years; P for Kruskal-Wallis test = 0.011). None of the 6 HIV-negative patients had a history of organ or hematopoietic stem cell transplantation. At the time of PEL diagnosis, 14 (74%) HIV-positive patients were on highly active antiretroviral therapy (HAART). Previous Kaposi sarcoma (KS) was present in 7 (28%) patients. None of the patients had pre-existing Castleman disease.

All patients had a lymphomatous effusion in ≥1 serous cavity, with pleural effusions being the most frequent (21/25; 84%), followed by peritoneal (14/25; 56%) and pericardial effusions (2/25; 8%). Ten (40%) patients had extracavitary PEL localizations in the following sites: lymph nodes (n = 7), bone marrow (n = 2), spleen (n = 2), mediastinum (n = 1), and rectum (n = 1). In 3 patients, the KS-associated herpesvirus/human herpesvirus 8 (KSHV/HHV-8) positivity was not determined in lymphomatous cells. One PEL was negative for KSHV/HHV-8. Epstein-Barr...
virus (EBV) positivity in lymphomatous cells was determined in 18 cases, of which 9 were EBV+. Of note, 1 HIV-negative patient had a CD20-positive PEL.

Information on treatment is shown in Table 1. Eight (28%) patients received no therapy. One patient received prednisone alone and one patient initiated HAART alone. Fifteen patients received first-line chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Of note, all 12 HIV-positive patients who received first-line chemotherapy were on HAART.

Three and four patients received CHOP with high-dose methotrexate (HD-MTX) and rituximab, respectively. In the group of patients who received CHOP with rituximab, 2 were HIV-negative and 2 HIV-positive. Of 15 patients, 9 (60%) who received first-line chemotherapy attained a complete or partial remission, of whom 3 ultimately relapsed. Further, 4 patients had progressive disease and in 2 the response was unknown. Six patients received second-line therapy, consisting of a variety of regimens (Table 1).

After a median follow-up of 7.6 (range, 0.1–142.3) months, 7 (28%) patients were still alive. The median follow-up for patients still alive was 38.2 (range, 14.1–142.3) months. The median OS for the entire cohort was 7.6 months and 1-year OS was 44% (95% confidence interval [CI], 24–62; Fig. 1A). For the 15 patients who received first-line chemotherapy, the median PFS was 14.7 months and 1-year PFS was 53% (95% CI, 26–74; Fig. 1B). The median OS and 1-year OS for these patients was 37.1 months and 59% (95% CI, 33–78), respectively (Fig. 1C).

This nationwide population-based study confirmed that PEL is a very rare aggressive lymphoma that primarily, but not exclusively, affects HIV-infected males. The patient survival in our contemporary study is equally poor as compared to the results described in the paucity of single- or multi-center studies. However, the incidence of PEL in the Netherlands is lower, as compared with a recent study from France covering the period 1996 to 2013. Likewise, the incidence of HIV in the Netherlands is lower, as compared to France (6.7 vs 8.4 per 100,000 persons in 2006–2015). Moreover, in 2014 to 2015, 1.4% of all newly diagnosed aggressive NHLs in the Netherlands were HIV-related (data not shown). Although the incidence of HIV-related aggressive NHLs is low in the Netherlands, it is apparent that HIV-infected individuals are still at elevated risk to develop HIV-related NHL in an era with contemporary HAART.

Our study shows, in line with prior studies, that prolonged survival can be achieved in selected patient subsets who can attain and maintain a remission after chemotherapy with HAART. In our series, only a minority of patients had HD-MTX added to first-line CHOP, as compared with a recent French series (20% vs 68%). In that French study, which also included PEL without serous cavity involvement (17/51; 33%), there was a hint that the addition of HD-MTX to CHOP(-like) therapy yielded similar OS than without HD-MTX addition. MTX tends to concentrate in the effusions, resulting in a delayed MTX clearance, which, in turn, may increase toxicity. On the other hand, the accumulation of MTX in the effusions might enhance anti-PEL activity. Therefore, in order to avoid severe systemic toxicity, adequate hydration, regular monitoring of MTX levels, and leucovorin rescue maintenance until complete MTX clearance should be applied to all patients in whom HD-MTX is added to CHOP(-like) therapy.

Table 1: Treatment Characteristics and Outcomes of Patients With Primary Effusion Lymphoma

| Patient No | Age | Sex | HIV+ | Type of Treatment | Outcome | Type of Treatment | Outcome | Survival, mo |
|------------|-----|-----|------|-------------------|---------|-------------------|---------|-------------|
| 1          | 46  | M   | No   | No therapy       | Death   |                   |         | 2.7         |
| 2          | 47  | M   | Yes  | CHOP             | Response unknown, death |         |         | 7.6         |
| 3          | 39  | M   | Yes  | 8× CHOP          | Response unknown, alive |         |         | 5.1         |
| 4          | 31  | F   | Yes  | No therapy       | Death   |                   |         | 0.1         |
| 5          | 30  | F   | Yes  | HAART only (initiated) | Other, relapse | 6× CHOP | PR, relapse, death | 15        |
| 6          | 64  | M   | Yes  | 3× CHOP          | Progression | 6× ifosfamide/etoposide | PR, death | 7.6         |
| 7          | 58  | M   | Yes  | 8× CHOP          | CR, alive |                   |         | 14.2+        |
| 8          | 31  | M   | Yes  | No therapy       | Alive   |                   |         | 74.8+        |
| 9          | 49  | M   | Yes  | No therapy       | Death   |                   |         | 0.3         |
| 10         | 59  | M   | Yes  | 3× CHOP and 3× MTX | CR, relapse | 1× DHAP | Progression, death | 5         |
| 11         | 53  | M   | Yes  | 8× CHOP          | CR, death |                   |         | 7.3         |
| 12         | 72  | M   | No   | 6× R-CHOP + 2R   | CR, relapse | 6× MTX | CR, relapse, death | 37.5       |
| 13         | 80  | F   | No   | No therapy       | Death   |                   |         | 2.1         |
| 14         | 63  | M   | Yes  | 3× R-CHOP        | Progression, death |         |         | 4           |
| 15         | 47  | M   | Yes  | No therapy       | Death   |                   |         | 0.1         |
| 16         | 67  | M   | No   | 8× CHOP          | PR, death |                   |         | 44.2        |
| 17         | 61  | M   | No   | 6× R-CHOP        | CR, alive |                   |         | 38.2+        |
| 18         | 44  | M   | Yes  | 4× CHOP21        | Progression | Radiotherapy and 2× CHOP | CR, alive | 14.1+        |
| 19         | 64  | M   | Yes  | Prednisone alone | Progression |                   |         | 3.2         |
| 20         | 38  | M   | Yes  | 3× CHOP14 and MTX | Progression | 1× VCD | Progression, death | 2.6        |
| 21         | 57  | M   | Yes  | 8× CHOP          | CR, relapse | 1× DHAP | Response unknown, death | 15.8       |
| 22         | 61  | M   | No   | No therapy       | Death   |                   |         | 0.7         |
| 23         | 48  | M   | Yes  | 8× CHOP          | CR, alive |                   |         | 24.3+        |
| 24         | 65  | M   | Yes  | No therapy       | Death   |                   |         | 9.4         |
| 25         | 51  | M   | Yes  | 8× R-CHOP21 and 6× MTX | CR, alive |         |         | 17.1+        |

= alive, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = CHOP without vincristine, CR = complete remission, DHAP = dexamethasone, high-dose cytarabine, and cisplatin, F = female, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, M = male, MTX = methotrexate, PR = partial remission, R = rituximab, VCD = bortezomib, cyclophosphamide, dexamethasone.
At present, only 1 study, which included 28 patients diagnosed in France between 1996 and 2003, aimed to identify prognostic factors in PEL. In that study, only poor performance status and absence of HAART before PEL diagnosis were independently associated with poor prognosis. Those outcomes, however, should be interpreted with caution, as the analyses were based on small patient numbers and largely covered a pre-HAART era. In the present study, covering a period with contemporary HAART and well-established NHL therapy, we did not attempt to assess prognostic factors due to the small patient numbers (n = 25). Collectively, it would be worthwhile to coalesce currently available studies into 1 large dataset to more robustly identify prognostic factors in PEL.

In summary, in an era with contemporary HAART and well-established NHL therapy, PEL is still associated with a poor prognosis. Nevertheless, particular patient subsets who can attain and maintain a remission after chemotherapy with HAART can enjoy prolonged survival. In the meantime, while we await on results from prospective intervention studies, information from population-based studies can support clinical decision making in PEL.

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