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Incidence, Clinic Presentation, and Outcomes of *Pneumocystis* Pneumonia when Utilizing Polymerase Chain Reaction-Based Diagnosis in Patients with Hodgkin Lymphoma

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Abstract

A Polymerase Chain Reaction-based diagnosis of *Pneumocystis* Pneumonia (PCP) and the need for anti-*Pneumocystis* prophylaxis in Hodgkin Lymphoma patients receiving chemotherapy requires further investigation. This retrospective, single-center, study evaluated 506 consecutive adult patients diagnosed with Hodgkin lymphoma receiving chemotherapy between January 2006 and August 2018. The cumulative incidence of PCP 1 year after start of chemotherapy was 6.2%

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Conceptualization and methodology: JNB, CAT, PMW, KCM, PKT, AHL; Data curation, formal analysis, and interpretation: JNB, CAT, PMW, KCM, AGP, ALP, PKT, AHL; Writing – original draft: JNB, CAT, PMW, KCM, AGP, ALP, PKT, AHL; Writing – review and editing: JNB, CAT, PMW, KCM, AGP, ALP, PKT, AHL. Guarantors of the work: JNB, CAT, AHL.

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(95% CI 3.8%–8.5%). Mortality 30 days from PCP diagnosis was 8% (n=2) with one death attributable to PCP. Bleomycin-containing combination chemotherapy regimen was not significantly associated with a higher risk for PCP when compared to other regimens (HR=1.59, 95% CI 0.55–4.62 p=0.40). Anti-pneumocystis prophylaxis was not significantly associated with a decreased incidence of PCP (HR=0.51, 95% CI 0.15–1.71, p=0.28). As the overall incidence is above the commonly accepted 3.5% threshold, clinicians should consider the potential value of prophylaxis. The utility of universal vs. targeted anti-pneumocystis prophylaxis requires prospective, randomized investigation.

Keywords

Pneumocystis jirovecii; Pneumonia; Hodgkin Lymphoma; Polymerase Chain Reaction; Trimethoprim; Sulfamethoxazole; Infection

Introduction:

Pneumocystis Pneumonia (PCP) is a life-threatening infection associated with high morbidity, mortality, and medical costs.[1–3] There are many risk factors associated with the development of PCP including HIV infection, underlying connective tissue diseases, solid organ transplantation, and hematopoietic stem cell transplantation.[4] Hematologic malignancy is also a risk factor for infection; however, the rate of infection is highly variable.[5–8] Different underlying diagnoses, varying baseline patient characteristics, and prescribed chemotherapy regimens influence risk of developing PCP. Certain chemotherapy combinations do not present an infection risk that is high enough to warrant routine anti-*Pneumocystis* prophylaxis according to contemporary thresholds.[5,8,9] However, there are chemotherapeutic regimens used to treat Hodgkin lymphoma that may increase the risk for PCP and make anti-*Pneumocystis* prophylaxis a potentially important component of the cancer management strategy.

The diagnosis of PCP is generally established by morphologically demonstrating *Pneumocystis* organisms from respiratory specimens by a variety of methods, including Giemsa or Giemsa-like rapid stains, Gomori methenamine silver stain, toluidine blue O stain, and fluorescein-conjugated monoclonal antibody (direct fluorescent-antibody [DFA] stain).[10] Studies have demonstrated that Polymerase Chain Reaction-based (PCR) amplification assay has an increased sensitivity when compared to DFA.[11–14] Our institution utilizes a quantitative PCR strategy that indicates the presence of pneumonia rather than colonization.[14] The use of PCR-based diagnostic techniques in the setting of clinical manifestations of respiratory compromise could improve the diagnosis of PCP in hematology patients and establish a contemporary incidence of PCP infection in the setting of Hodgkin lymphoma. This allows for an accurate reevaluation of the need for antimicrobial prophylaxis.

Overall, the risk of PCP infection in hematologic patients, particularly in the setting of a PCR-based diagnosis, has not been adequately defined, and the incidence of PCP during chemotherapy for Hodgkin lymphoma patients is unknown.[15–18] Therefore, the necessity for prophylaxis in this population remains unclear. Intolerance to prophylaxis regimens is

not uncommon; thus, routine prophylaxis should be limited to populations with a fixed high incidence of PCP.[19] The objective of this study is to examine the relationship between the management of Hodgkin lymphoma and the development of PCP when infection is diagnosed using our PCR-based technique. Results from this investigation will provide additional information surrounding the need to provide prophylaxis for patients prescribed therapy for Hodgkin lymphoma.

Methods:

This single-center, retrospective, cohort study was approved by the Mayo Foundation Institutional Review Board and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki with adherence to all relevant regulations of the United States Health Insurance Portability and Accountability Act. Consecutive, adult patients diagnosed with Hodgkin lymphoma between January 2006 and August 2018 were evaluated for inclusion. Patients who were less than 18 years of age at diagnosis, had a previous bone marrow or stem cell transplantation, had a documented HIV infection or a history of HIV seropositivity, denied Minnesota research authorization, were pregnant or incarcerated were excluded.

An electronic chart review was performed for all patients included in the study from date of diagnosis up to 180 days after the last chemotherapy administration for a diagnosis of PCP. Baseline demographic data was abstracted between Hodgkin lymphoma diagnosis with subtyping according to World Health Organization (WHO) classification criteria and prior to systemic chemotherapy. Lymphoma diagnosis was determined by tissue biopsy, lymph node biopsy or bone marrow morphology, Fluorescence in situ hybridization, cytogenetic and molecular techniques. Information regarding the administration of chemotherapy, including drug doses and administration dates, was collected from a clinical document management reports program.

The diagnosis of PCP was defined as a positive single copy gene targeted, non-nested real-time, *Pneumocystis* PCR result from any respiratory sample resulting concurrently with clinical signs and symptoms of pulmonary compromise. The initial development and the quantitative PCR methods and conditions were described previously and set a quantitative threshold at 45 cycles.[11] This assay differs from many other published methods of PCR diagnosis, in that the detection threshold was set to detect active PCP infection and does not appreciably detect colonization with *Pneumocystis* organisms.[14] The degree of hypoxemia was defined by the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) [PF] ratio or the saturation of arterial oxygen (SaO_2): FiO_2 (SF) ratio when arterial blood gas data were not available. Mortality was defined as a death occurring within 30 days of PCP diagnosis.

Data pertaining to patient demographics and clinical characteristics are summarized with descriptive statistics. These included counts and percentages for categorical and ordinal variables and medians and interquartile ranges (IQR) for continuous variables. Cox proportional hazard modeling (with 95% confidence interval bands) was used to demonstrate the strength of association between the independent variables and adverse event rate. All

analyses were carried out using the JMP statistical software package (Version 9.0, SAS Institute Inc., Cary, NC). A *P* value less than 0.05 was considered statistically significant.

Results:

The 506 included patients had a median (IQR) age of 40.3 (28.6, 59.7) years, 287 (56.7%) were male, and 470 (92.9%) were Caucasian. A majority (n=411, 81%) of patients were newly diagnosed, while 95 (19%) patients received chemotherapy for relapsed disease. There were 47 (9%) patients prescribed other immunosuppressive medications, alone or in combination, for other conditions prior to their cancer diagnosis. Prednisone was the most frequent additional immunosuppressant (n=30), followed by oral methotrexate (n= 5), and tacrolimus (n=5). Further baseline demographics and clinical characteristics are described in table 1 with no significant differences between those diagnosed with and those free from PCP.

Chemotherapy combined with radiation therapy was prescribed for 163 (32.2%) patients while 343 (67.8%) patients received chemotherapy alone. Chemotherapy regimen distribution included 356 patients (70.4%) receiving bleomycin-containing chemotherapy with the treatments outlined in table 2. The median (IQR) total Bleomycin dose was 122 (IQR: 78, 178) units with 176 (49%) patients prescribed 12 doses of bleomycin, or 6 full cycles of Adriamycin, Bleomycin, vinblastine, and dacarbazine (ABVD).

Anti-pneumocystis prophylaxis was provided for 97 patients (19%; n=39 *a priori*, 58 after chemotherapy initiation). Trimethoprim-sulfamethoxazole (TMP-SMX) was the preferred agent prescribed at a variety of different doses and schedules for 90 (93%) patients at provider discretion, followed by aerosolized pentamidine (n=3), dapsone (n=3), and atovaquone (n=1). Two infections occurred in patients receiving anti-pneumocystis prophylaxis. One patient was prescribed TMP-SMX and 1 patient was prescribed monthly aerosolized pentamidine. Interestingly, anti-pneumocystis prophylaxis was not significantly associated with a decreased incidence of PCP (HR=0.51, 95% CI 0.15–1.71, p=0.28).

The cumulative incidence of PCP 1 year after start of chemotherapy was 6.2% (95% CI 3.8%–8.5%) as shown in figure 1 (n=26 PCP events overall). The median (IQR) duration of follow up was 6.4 (4.0, 8.1) months. Diagnosis of PCP occurred most commonly during the 2nd (n=8, 30.7%), 3rd (n=8, 30.7%), and 4th (n=7, 26.9%) cycles of chemotherapy. Twenty-four patients were not prescribed anti-*pneumocystis* prophylaxis at the time when PCP was diagnosed. TMP-SMX was the only agent prescribed as PCP treatment. Mortality 30 days from PCP diagnosis was 8% (n=2) with one death attributable to PCP infection.

The median SF ratio at the time of diagnosis was 429 (325, 452) and among those with arterial blood gas data (N = 11), the PF ratio was 211 (102, 267). On presentation, appropriate oxygenation (SaO₂ > 90%) was maintained without any supplemental oxygen in most patients (N = 23; 60.5%). The remainder required immediate application of nasal cannula (N = 14; 36.8%) or closed face mask (N = 1; 2.6%). Eight patients (21.1%) required ICU admission, 6 of which required endotracheal intubation and support of the mechanical

ventilator for a median 4.5 (2.1, 11) days. The median ICU and hospital lengths of stay were 3.9 (1.4, 7.4) and 3.9 (2.6, 6.7) days, respectively.

Bleomycin-related lung compromise was suspected in 131 (25.9%) patients. Of those with suspected bleomycin-related lung compromise, 38 (29.2%) required hospital admission. Twelve patients were found to have a positive *Pneumocystis* PCR within 72 hours of hospitalization. Bleomycin-containing combination chemotherapy was not significantly associated with a higher risk for PCP when compared to other combination regimens (HR=1.59, 95% CI 0.55–4.62 p=0.40).

Discussion:

Results of our study demonstrate a 6.2% incidence of PCP infection diagnosed via PCR among patients with Hodgkin Lymphoma being actively treated with chemotherapy or chemotherapy combined with radiation therapy. Only 7.7% of patients received a priori anti-*Pneumocystis* prophylaxis, while an additional 11.5% were initiated on prophylactic therapy sometime after starting chemotherapy. Interestingly, anti-*Pneumocystis* prophylaxis was not significantly associated with a decreased incidence of PCP. Although 38% of patients who were positive for PCP required ICU admission, only 2 deaths were attributable to infection.

A 6.2% incidence was somewhat unexpected in our patient population. PCP infection is a disease associated with T-cell deficiency and lymphocyte depletion, particularly CD4+ T-lymphocytes, while Hodgkin lymphoma is an uncommon B-cell lymphoid malignancy.[20–23] Other B-cell lineage subtypes have demonstrated a low incidence of PCP infection, while studies that demonstrated a higher incidence have attributed the increased rates to intensive combination chemotherapy treatments or high-dose steroids.[5–7,17,24,25] Hodgkin and Reed-Sternberg (HRS) cells are of B-cell lineage, but are generally embedded in a microenvironment of inflammatory cells, including different types of T-cells and macrophages.[26] HRS cells have been shown to inhibit an effective immune response and interfere with the proper T-cell immune function, especially CD4 T-lymphocytes.[26,27] Whether the complex interplay between T-cells and the Hodgkin lymphoma containing microenvironment is responsible for the rate of PCP infection is unknown.

Data currently defining PCP rates in patients receiving treatment for Hodgkin lymphoma is limited to epidemiologic studies comprised of multiple hematologic malignancies, historical trials, and case reports.[4,16,18,28–30] There is a presumed “moderate” risk for PCP infection due mainly to the administration of the regimen ABVD; however, it was listed as a grade “D” recommendation and the primary reference for this categorization was a case report.[16,31] Contemporary trials of Hodgkin lymphoma patients receiving ABVD report few overall infections and fail to mention PCP as a major contributing pathogen, even in the elderly population.[32–34] Additionally, the ABVD regimen was found to be significantly less lymphotoxic than other chemotherapy combinations, particularly those containing cyclophosphamide or pyrimidine analogs.[35]

It has been previously reported that when the estimated risk of PCP exceeds 3.5%, a mortality benefit is observed when prophylaxis is utilized.⁹ The findings of this study would suggest routine prophylaxis with TMP-SMX would be appropriate based solely on the rate of observed infection. Notably, our analysis did not associate anti-*Pneumocystis* prophylaxis with a significant decrease in incidence of PCP infection. It is unclear why the use of PCP prophylaxis did not result in a significantly decreased incidence of infection. TMP-SMX appears to be the most effective agent in preventing PCP infection and PCP rates of less than 1% have been reported in several studies where TMP-SMX prophylaxis was prescribed to cancer patients.[17,36–39] Limited head-to-head studies have been conducted comparing the efficacy of once-daily, twice-daily, or three times-weekly dosing.[37,40] The frequency of aerosolized pentamidine has also been questioned.[41] One patient who experienced a breakthrough PCP infection was prescribed TMP-SMX while 1 patient was prescribed monthly aerosolized pentamidine. It is possible that patients included in our study were either non-compliant with their medications or prescribed anti-*Pneumocystis* prophylaxis on a less favorable schedule.

Another possible hypothesis for the incidence and apparent ineffectiveness of anti-*Pneumocystis* prophylaxis found in our study is the overlap of clinical presentation between bleomycin-induced pulmonary compromise and active PCP infection leading to detection bias.[42,43] Pulmonary injury after bleomycin is a well-known and commonly occurring complication appreciated since the discovery of its antitumor efficacy decades ago.[44] Provider awareness of, and sensitivity to, the morbidity and mortality associated with bleomycin-lung toxicity and PCP infection will likely compel a conservative approach towards patient care and intense observation. The clinical presentation of either condition will include non-specific symptoms of dyspnea, cough, and chest pain prompting further aggressive examination[10,45]. Imaging with a chest radiograph or computed tomography scan and invasive sampling, particularly by bronchoalveolar lavage, are needed to rule out infection or progression of malignancy.[10] Therefore, it is possible that a patient admitted with bleomycin-induced pulmonary compromise may have incidental detection of *Pneumocystis* organisms. The overlap in clinical presentation of these syndromes may lead to over-identification of *Pneumocystis* colonization, subsequent misdiagnosis, and unnecessary treatment of PCP. This could potentially falsely elevate the true rate of pathologic PCP.

Despite the potential benefits prophylaxis may introduce, additional considerations should be made when determining whether to employ anti-pneumocystis prophylaxis, particularly with first-line TMP-SMX. Considerations for TMP-SMX include sulfonamide allergies and hypersensitivity, renal or hepatic abnormalities, possible myelosuppression, and drug interactions.[47–49] Desensitization protocols have been successfully implemented to ensure optimal therapy in patients reporting hypersensitivities.[38,50,51] While myelosuppression is considered a side effect of TMP-SMX based on historical studies, more recent studies have not demonstrated the same degree of myelosuppression, likely due to improvements in chemotherapy regimens, as well as the use of granulocyte colony-stimulating factors.[52]

Limitations of this study include the retrospective, non-randomized design and dependence on the accuracy of electronic medical records. While patients were managed initially at our institution, it is possible that those who referred from a distant facility returned home during the immediate follow up period after the last treatment and incurred an infection that was not captured. We attempted to enroll consecutive patients over a substantial timeframe to establish an appropriately representative sample for analysis. As stated previously, our investigation was predicated on a diagnosis achieved using a PCR-based technique. While our PCR assay has been designed to minimize the detection of *Pneumocystis* colonization, the possible detection of some cases with colonization possibly could have resulted in overestimation of the overall incidence of *Pneumocystis* infection. Despite all cases of *Pneumocystis* PCR positivity on respiratory samples being verified through electronic medical record review to establish a clinical course and outcome consistent with clinical PCP, the confounding by bleomycin-related pulmonary compromise must be acknowledged and cannot be isolated given its frequency of occurrence. Lastly, it should be noted that the decision to use anti-*Pneumocystis* prophylaxis was left entirely up to physician discretion, since defined guidelines in this patient population were not previously available. Similarly to detection of *Pneumocystis* infection, bleomycin-related pulmonary compromise may compromise our ability to determine the true efficacy of anti-*Pneumocystis* prophylaxis.

Conclusion:

Patients receiving combination chemotherapy for treatment of Hodgkin Lymphoma experienced a 6.2% incidence of PCR-diagnosed PCP infection. As the incidence is above the 3.5% threshold previously described, the clinician should consider the potential value of prophylaxis. Anti-*Pneumocystis* prophylaxis was not significantly associated with a decreased incidence of PCP in our study; however, defining the overall utility of a universal versus targeted anti-*Pneumocystis* prophylaxis strategy, the best anti-*Pneumocystis* agent, and optimal timing for prophylaxis requires further investigation.

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Disclosures:

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Figure 1. Cumulative incidence and 95% confidence bands of PCP 1 year after start of chemo in patients with Hodgkin lymphoma receiving chemotherapy.

Table 1.
Summaries of baseline demographics and laboratory values of Hodgkin lymphoma patients with occurrence of PCP infection.

Characteristic	Patients (N=506)	Patients with PCP (N=26)	Patients without PCP (N=480)
Age, median (IQR)	40.3 (28.6–59.7)	36.6 (28.7–55.3)	40.3 (28.5–59.8)
Male, No. (%)	287 (56.7%)	15 (57.7%)	272 (56.7%)
Race, No. (%)			
Caucasian	470 (92.9%)	24 (92.3%)	446 (92.9%)
Other	36 (7.1%)	2 (7.7%)	34 (7.1%)
Body Surface Area, median (IQR)	2.0 (1.8–2.2)	2.0 (1.9–2.1)	2.0 (1.8–2.2)
LVEF (%), median (IQR)	62 (58–65)	63.5 (61–65)	62 (58–65)
Hodgkin lymphoma subtype, No. (%)			
Nodular lymphocyte predominant Hodgkin lymphoma	41 (8.1%)	1 (3.8%)	40 (8.3%)
Classical Hodgkin lymphoma, NOS	136 (26.9%)	5 (19.2%)	131 (27.3%)
Nodular sclerosis classical Hodgkin lymphoma	295 (58.3%)	18 (69.2%)	277 (57.7%)
Lymphocyte-rich classical Hodgkin lymphoma	10 (2.0%)	0 (0.0%)	10 (2.1%)
Mixed cellularity classical Hodgkin lymphoma	23 (4.5%)	2 (7.7%)	21 (4.4%)
Unclassifiable Hodgkin lymphoma	1 (0.2%)	0 (0.0%)	1 (0.2%)
Type of Diagnosis, No. (%)			
Primary	411 (81.4%)	25 (96.2%)	386 (80.6%)
First Relapse	72 (14.3%)	1 (3.8%)	71 (14.8%)
More than first relapse/Unknown	22 (4.4%)	0 (0.0%)	22 (4.6%)
Lymphoma Stage, No. (%)			
I	29 (5.7%)	0 (0.0%)	29 (6.0%)
II	203 (40.1%)	9 (34.6%)	194 (40.4%)
III	101 (20.0%)	5 (19.2%)	96 (20.0%)
IV	120 (23.7%)	11 (42.3%)	109 (22.7%)
Unstaged/Unknown	53 (10.5%)	1 (3.8%)	52 (10.8%)
Bone Marrow Involvement, No. (%)	61 (12.2%)	3 (11.5%)	58 (12.2%)
Percent involvement, median (IQR)	22.5 (10–50)	30 (10–50)	22.5 (10–50)
Serum Creatinine, mg/dL, median (IQR)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.8 (0.7–1.0)
Estimated Creatinine Clearance, No. (%)			

Characteristic	Patients (N=506)	Patients with PCP (N=26)	Patients without PCP (N=480)
< 30 ml/min	4 (0.8%)	0 (0.0%)	4 (0.8%)
31–60 ml/min	30 (6.0%)	0 (0.0%)	30 (6.4%)
> 60 ml/min	463 (93.2%)	26 (100.0%)	437 (92.8%)
Hemoglobin, median (IQR)	12.7 (10.9–13.9)	12.7 (10.9–13.5)	12.7 (10.9–13.9)
WBC count, $\times 10^9/L$, median (IQR)	8.1 (6.1–10.9)	6.4 (5.6–12.4)	8.2 (6.2–10.9)
ANC count, median (IQR)	5.6 (3.8–8.3)	4.4 (3.7–9.2)	5.7 (3.9–8.3)
ALC count, median (IQR)	1.3 (0.9–1.8)	1.1 (0.8–1.8)	1.3 (0.9–1.8)
Aspartate Aminotransferase, median (IQR), (N=416)	23 (17–30)	23 (16–30)	23 (17.5–30)
Alanine Aminotransferase, median (IQR), (N=184)	24 (16–36)	28 (14–36)	23 (16–36)
Alkaline Phosphatase, median (IQR), (N=411)	96 (79–127)	85 (72–117)	97 (79–127)
Total Bilirubin, median (IQR), (N=417)	0.5 (0.3–0.6)	0.3 (0.3–0.5)	0.5 (0.3–0.7)
LDH, median (IQR), (N=473)	190 (159–236)	198 (183–243)	189 (159–235)
Albumin, mg/dL, median (IQR), (N=320)	4.1 (3.6–4.4)	4.1 (3.7–4.5)	4.1 (3.6–4.4)

Abbreviations: CI: Confidence interval; IQR: interquartile range

[†]Hazard ratios for continuous variable are per 1 unit increase

Table 2.

Chemotherapy regimen distribution prescribed to Hodgkin Lymphoma patients as induction therapy for new diagnosis or relapsed disease

Chemotherapy regimen	Number of patients (%)
Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD)	364 (72)
Ifosfamide, Carboplatin, Etoposide (ICE)	33 (6.5)
ABVD + monoclonal antibody	15 (3)
Brentuximab Vedotin-based chemotherapy	13 (2.5)
Carmustine, Cyclophosphamide, Vinca Alkaloid, Procarbazine, Prednisone (BCVPP)	10 (2)
Gemcitabine-based chemotherapy	10 (2)
Mechlorethamine, Vincristine, Procarbazine, Prednisone (MOPP)-based chemotherapy	8 (1.5)
Other regimen	53 (10.5)