Published in final edited form as:

Clin Breast Cancer. 2012 April ; 12(2): 138–141. doi:10.1016/j.clbc.2011.10.003.

PCP in an Atypical Host

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Introduction

Pneumocystis jiriveci pneumonia (PCP) is an opportunistic fungal pathogen of the lungs. First diagnosed as a cause of pneumonia among premature and malnourished infants in the post-World War II era, it is now typically seen in immunocompromised hosts, like patients with human immunodeficiency virus (HIV) with T-helper cell counts (CD4) less than 200 (cells/millimeter³) or patients with hematologic malignancies.^{1,2} However, PCP is rare in the solid tumor population.

Case Report

A 47-year-old woman with breast cancer metastatic to the lung was started on a Phase I trial of monthly bendamustine and erlotinib with dexamethasone pre-medication.³ The trial included patients with metastatic estrogen receptor (ER), progesterone receptor (PR) and HER2 negative breast cancer. In the study's first phase, selected patients were given bendamustine 100 or 120 mg/m² IV day 1 and 2, as well as erlotinib 100 or 150 mg po days 5 through 21 of a 28-day cycle. The anti-emetic regimen included 12 mg of oral dexamethasone once daily on days 1 and 2 followed by 4 mg twice-daily days 3 and 4. Patients were evaluated every 2 cycles (8 weeks) for treatment response. If no disease progression was appreciated following 6 cycles of combination therapy, patients were started on erlotinib 150 mg po daily. Our patient achieved stable disease after two cycles on the trial and continued on this regimen for six total cycles. Upon completion of the sixth cycle, restaging CT studies demonstrated disease progression in the liver and new ground-glass opacities throughout her lungs (Figure 1). Given cancer progression, she started a new regimen with paclitaxel and bevacizumab. Just prior to the start of this regimen, she developed cough and dyspnea and was treated with azithromycin for presumed bronchitis. Her symptoms persisted and she was prescribed levofloxacin and chemotherapy was delayed one week. After antibiotic therapy, she clinically improved and cycle 1 of weekly paclitaxel 90mg/m² and bevacizumab 15mg/m² was administered with 10 mg of dexamethasone premedication. Three days after the start of chemotherapy, her dyspnea acutely worsened

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Prior Presentations: Ohio ACP Annual Scientific Meeting, Columbus, OH. October 1, 2010. Resident Poster Session.

Conflict of Interest

Dr Layman received research funding from the NCCN to conduct the clinical trial. All other authors state that they have no conflicts of interest.

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and she was referred to the emergency department. There, she was tachycardic and hypoxic with ambulation to 88% on room air. An arterial blood gas on ambient air revealed a PaO₂ of 35 mmHg and A-a gradient of 63. A CT pulmonary embolus (PE) showed no PE, but reimaged the previously noted ground-glass opacities. Laboratory studies demonstrated normal neutrophils but profound lymphopenia (absolute lymphocyte count (ALC) 100). Bronchoscopy showed *Pneumocystis jiriveci* in the bronchealveolar lavage (Figure 2). CD4 count was 14; HIV and RNA viral loads were negative. After initiation of oral trimethoprim and sulfamethoxazole (TMP-SMX), she developed worsening hypoxia. Steroids and immunoglobulin transfusion were administered. She improved in one week and completed a 21-day course of TMP-SMX followed by daily prophylaxis. Since discharge, CD4 counts initially improved but remained below 200. Repeat chest CT showed resolution of ground-glass opacities. Unfortunately, despite compliance with TMP-SMX therapy, the patient decompensated approximately four months later and died from overwhelming sepsis and acute respiratory distress syndrome (ARDS). Importantly, her CD4 count had still not improved by that time, remaining at a value just over 100 (Figure 3).

Discussion

PCP infection is not as common in the solid tumor population compared to rates in hematologic malignancy.⁴ Among solid tumor cases reported, many involve patients with metastatic brain cancer receiving high-dose steroid therapy.^{5,6} Despite the increased prevalence of breast cancer, there are surprisingly few case reports of PCP infection in breast cancer patients. One review found only 24 documented cases of PCP in breast cancer patients from 1970 to 1996, and the majority had received steroids.⁷ A case series from Mayo Clinic of 116 consecutive non-HIV-infected patients noted that in 91% of patients, steroid therapy had been given within one month of diagnosis of PCP. The median dose equivalent was 30 mg/d and median duration of steroid therapy before PCP development was 12 weeks.⁸ Our patient received steroids at the beginning of each treatment cycle, which may have contributed to PCP infection.

In addition to steroid use, other risk factors for PCP include lymphopenia, dose intensity of chemotherapy and certain chemotherapeutic agents capable of inducing lymphopenia. Tolaney et al⁹ described two breast cancer patients who developed PCP after receipt of dose-dense chemotherapy with doxorubicin/cyclophosphamide followed by paclitaxel. Another report describes PCP in two women with stage II breast cancer treated with adjuvant vinblastine, fluorouracil (5-FU), cyclophosphamide, and doxorubicin or adjuvant cyclophosphamide, 5-FU, and doxorubicin alone. These individuals were found to have profound lymphopenia and reversed CD4/CD8 ratios, with CD4 counts of 128 and 180.¹⁰

Our patient received bendamustine, an alkylating nitrogen mustard derivative capable of inducing reversible B and T cell lymphocytopenias, affecting both CD4- and CD8-positive cells.^{11,12} In chronic lymphocytic leukemia (CLL), a disease in which bendamustine use is FDA approved, several studies have evaluated the maximal tolerated dose and dose-limiting toxicities associated with bendamustine. A phase I/II study in relapsed or refractory CLL patients who received a median of three prior regimens (50% received fludarabine) and who were later given bendamustine reported grade 3/4 leukopenia and grade III/IV infection in a respective 50% and 43% of patients. Two patients died of atypical pneumonia.¹³ Another phase I/II study of bendamustine in fludarabine naive patients with CLL reported grade III/IV leukopenia in only 20% of recipients.¹⁴ In a randomized trial of CLL patients receiving either single-agent bendamustine or fludarabine, the bendamustine arm was associated with a higher incidence of hematologic toxicity, but the rate of grade III/IV infections was nearly equal in both arms, approximately 15%.¹⁵ A phase III multicenter study with previously untreated CLL patients randomized to either bendamustine or chlorambucil treatment

reported more frequent grade III/IV neutropenia and anemia in the bendamustine arm, but low rates of severe infection (grades III/IV) in both groups (8% versus 3% in bendamustine versus chlorambucil).¹⁶ In retrospect, our patient's ALC was normal before bendamustine therapy. Counts decreased to 900 after one treatment cycle and continued to decrease even after bendamustine discontinuation, with the nadir 30 after 6 total cycles. Bendamustine's severe myelosuppressive effects were similarly implicated in another report of PCP in an advanced breast cancer patient after bendamustine monotherapy.¹⁷ Finally, our patient received bendamustine combined with erlotinib; we suspect this combination may have enhanced the patient's lymphopenia. There has been report of PCP infection in a patient with glioblastoma multiforme receiving erlotinib in combination with temozolomide, though it is unclear if the patient was lymphopenic at the time.¹⁸

Like HIV patients, lymphopenia may place cancer patients at increased risk for opportunistic infections such as PCP. However, in contrast to the HIV population, there is little consensus regarding the appropriate initiation of PCP prophylaxis in non-HIV patients receiving immunosuppressive therapies.¹⁹ In a meta-analysis of randomized controlled trials of PCP prophylaxis in immunocompromised patients without HIV, the meta-analysis concludes that PCP prophylaxis is indicated when the risk of PCP is greater than 3.5% in adults.²⁰ Festic et al suggest PCP prophylaxis be strongly considered for all immunosuppressed non-HIV patients, especially if receiving >16mg/d prednisone or other cytotoxic therapy.²¹ A retrospective analysis proposed prophylaxis in patients with acute lymphocytic leukemia, those undergoing bone marrow transplantation or if receiving corticosteroids with > 20mg prednisolone equivalents for >1 month.²² Critics of prophylaxis suggest prophylaxis may create PCP drug resistance or unnecessarily expose patients to therapy-associated side effects without evidence of definite benefit.²³ In our patient, PCP prophylaxis was only given after initial infection. Unfortunately, when compared to HIV-patients, those with solid tumor malignancy and concurrent PCP present atypically, decompensate rapidly as in our case, and have high mortality rates, making timely recognition of this infection critical.⁶ A retrospective review of outcome patterns for AIDS-related and non-AIDS-related PCP infection between 1985 to 1995 confirms this finding. The study noted that the mortality rate for HIV patients with PCP decreased during the study period (11.7 to 6.6%), while the rate for non-HIV patients remained much higher (39%).²⁴ This observation emphasizes the need to better characterize the selection criteria for prophylaxis recipients so as to prevent primary infection.

When caught early, PCP can be effectively treated with several therapies, most notably TMP-SMX. Major limitations of TMP-SMX are typically its side effects, including allergic reactions and myelosuppression. Significant reductions in both absolute neutrophil and lymphocyte counts have been demonstrated in children with acute lymphoblastic leukemia in clinical remission.²⁵ When used for prophylaxis in autologous bone marrow transplantation recipients, neutrophil recovery time was also more prolonged than recovery in patients receiving fluoroquinolones.²⁶ However, significant myelosuppression was not reported in the original investigations of TMP-SMX as prophylactic therapy.^{27,28} Typically, treatment is given for a total of 21 days. Systemic steroids are often added if the patient is hypoxic or with an A-a gradient > 35 mmHg. Unfortunately, large-scale trials in the non-HIV population are lacking to validate these guidelines.

Conclusion

This case describes PCP infection in a woman with metastatic breast cancer after treatment with bendamustine, a chemotherapeutic agent associated with profound lymphopenia. Additional investigation is needed to define the solid tumor population most at risk for PCP infection and to identify those who might benefit from prophylaxis.

Acknowledgments

Acknowledgements of Research Support: This study was approved and funded by the National Comprehensive Cancer Network (NCCN) from general research support provided by Cephalon, Inc.

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Clinical Practice Points

Pneumocystis jiriveci pneumonia (PCP) commonly manifests in the immunocompromised host with human immunodeficiency virus (HIV) or hematologic malignancies. PCP infection in the solid tumor population is a rare phenomenon, particularly in patients with breast cancer. We describe a case of PCP in a metastatic breast cancer patient after treatment with bendamustine, a chemotherapeutic agent associated with profound lymphopenia. In the solid tumor population, risk factors for PCP include lymphopenia, steroid use, dose intensity of chemotherapy, and certain chemotherapeutic agents like bendamustine, which can cause lymphopenia. As demonstrated by our patient, those with solid tumor malignancy and concurrent PCP present atypically, decompensate rapidly, and have high mortality rates, underscoring the importance of making a timely diagnosis. We will discuss the need to better characterize those non-HIV immunocompromised patients who have profound and persistent lymphopenia and whom may benefit from prophylaxis.

Figure 1.
Computed tomography (CT) of the chest demonstrating new ground-glass opacities throughout the lungs, concerning for atypical infection

Figure 2.
Bronchoalveolar lavage demonstrating *Pneumocystis jirovecii*

Figure 3.
Progression of CD4 and absolute lymphocyte count after treatment with bendamustine