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Pneumocystis jirovecii pneumonia prophylaxis during temozolomide treatment for high-grade gliomas

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Contents

Abstract

High-grade glioma patients receiving concomitant chemoradiotherapy with temozolomide 75 mg/m^2 during six to seven weeks or dose-dense temozolomide regimens especially in combination with chronic use of corticosteroids have a high risk for developing *Pneumocystis jirovecii* pneumonia. In this review, we define risk groups and propose a guideline for prophylaxis using risk stratification.

Keywords: *Pneumocystis jirovecii*; Prophylaxis; Temozolomide; High-grade glioma

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1. Introduction

High-grade gliomas are the most common and most malignant variant of gliomas, with a median survival of 12–15 months for glioblastoma [1,2]. Concomitant chemoradiotherapy with temozolomide 75 mg/m^2 followed by 6 postradiation courses temozolomide 150–200 mg/m^2 day 1–5 every 4 weeks is currently the standard of care in newly diagnosed glioblastoma patients [3]. Patients with primary brain tumors have an increased risk of developing *Pneumocystis jirovecii* pneumonia (PcP). Untreated glioma patients have an overall incidence PcP rate of 1% with a mortality rate of more than 50% [4,5]. Predisposing factors for acquiring PcP are the disease itself, use of corticosteroids, radiotherapy and chemotherapy. However, general administration of prophylactic antibiotics in every high-grade glioma patient treated with temozolomide and radiotherapy need to be reconsidered in light of possible toxicity and drug interaction. In this review, we define risk groups and propose a guideline for prophylaxis using risk stratification. Within the high-grade glioma patient population, the group of patients with glioblastoma is studied the most. Therefore, we have used this patient model, with an extrapolation for anaplastic astrocytoma patient group for this review.

2. Search strategy

Data for this review were identified by Medline searches using various combinations of the search terms 'chemotherapy', 'temozolomide', 'brain tumor', glioblastoma', 'glioma', '*Pneumocystis*', 'opportunistic infections', 'primary prophylaxis', 'immune' and 'immunosuppression'. Only papers published in English were included. Additional references were selected from relevant articles. Abstracts and reports from meetings were included only when they related directly to previously published work. Eventually, 755 articles were screened of which 63 articles remained after screening by abstract on subject matter and study methodology.

3. *Pneumocystis jirovecii* pneumonia

P. jirovecii, formerly known as *Pneumocystis carinii*, is an opportunistic organism causing life-threatening pneumonia, especially in immunocompromised individuals [6]. Person-to-person transmission occurs by airborne route [7]. Over half of the general population is infected asymptomatically and become a reservoir spreading the infection to more vulnerable patients [8–10]. Symptoms in human immunodeficiency virus (HIV)-negative patients are severe respiratory failure associated with progressive shortness of breath, dry cough and low-grade fever [6]. Often, physical examination reveals tachypnea, hypoxemia, tachycardia and normal or near-normal lung auscultation. Patients at risk for PcP are

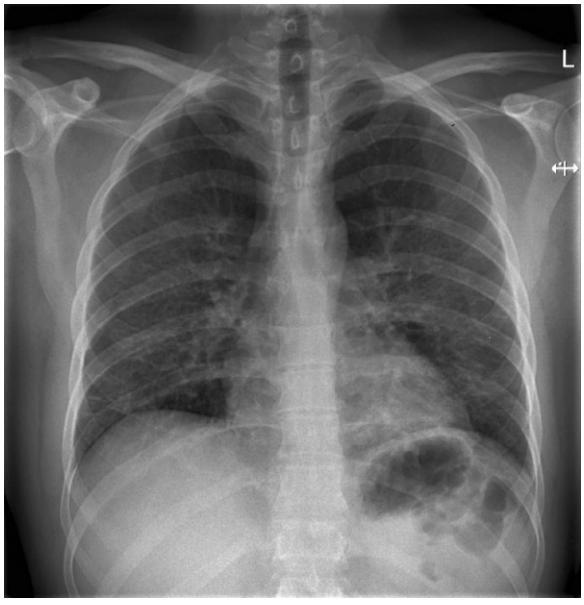

Fig. 1. Chest X-ray of a previously healthy 23-year-old man presenting with slowly progressive dyspnea, a dry cough and fever shows bilateral interstitial changes, more obvious in both lower lobes. He was diagnosed with PcP and HIV with a CD4-count of 50.

HIV-positive patients with a low CD4+ count who do not yet receive antiretroviral therapy over a prolonged period of time, solid-organ transplantation recipients, patients with connective tissue disease or other rheumatologic disease, patients with inflammatory bowel disease, and patients with hematological or solid malignancies [9,11–19]. Incidence and mortality rates can vary greatly, emphasizing the importance of identifying risk factors [4–6,9,11,20]. In contrast to HIV-positive patients, HIV-negative patients with PcP are older (respectively, 42 ± 15 vs. 68 ± 13 years), and have an underlying pulmonary disease twice as often [21]. Time span between onset of symptoms and start of PcP treatment is shorter in HIV-negative patients. Mortality from PcP due to acute respiratory failure in patients with HIV is approximately 10–20% compared with 35–50% in those without HIV [5,22,23]. Radiological findings vary from typical diffuse, bilateral, interstitial infiltrates to cavitary nodules, and even pneumothorax. Most frequently, symmetric, atypical ground glass opacities in the perihilar and lower zones with perihilar sparing are observed [24] (Fig. 1). Diagnosis can be made by microscopic staining or polymerase chain reaction (PCR) techniques [6]. Staining delineates *P. jirovecii* cyst forms in sputum or bronchoalveolar lavage (BAL) fluid [25]. Trophic and cyst forms can be detected by direct antigen immunofluorescence. In patients with a high risk for respiratory failure, endotracheal aspirates can be used for sampling instead of BAL fluid. PCR techniques have higher sensitivity rates varying between 70 and 88% compared to microscopy. Quantitative real-time PCR is more accurate in distinguishing between PcP and *P. jirovecii* colonization with lower turnaround times and less risk for run-to-run contamination [26,27]. Quantitative PCR techniques need to be validated as