Pneumocystis jirovecii prophylaxis in patients treated for high-grade gliomas: a survey among neuro-oncologists

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Abstract

Background. Pneumocystis jirovecii pneumonia (PJP) is a known complication in patients with high-grade gliomas (HGGs) who are treated with radiation and chemotherapy. PJP prophylaxis is commonly recommended, but there are currently no clear guidelines regarding duration of treatment and choice of drugs. This study aimed to assess current practice patterns of PJP prophylaxis among neuro-oncologists.

Methods. An online survey of 14 multiple choice questions was sent to 207 neuro-oncologists and medical oncologists treating brain cancers at all National Cancer Institute-designated cancer centers in the United States. Recipients were identified via a search of the cancer centers’ websites.

Results. Sixty-one invited experts completed the survey (response rate 29%; of these, 72% were neuro-oncologists, 18% were medical oncologists, and 10% were pediatric neuro- or medical oncologists). Seventy percent of respondents stated that they routinely prescribe PJP prophylaxis, while 7% do not provide prophylaxis. Eighty-one percent of respondents use absolute lymphocyte count (ALC) to assess lymphopenia and 13% also monitor CD4 lymphocyte counts during prophylaxis. The most commonly used first-line agent is trimethoprim-sulfamethoxazole (88% of respondents), followed by pentamidine (6%). Discontinuation of PJP prophylaxis is determined by the following: count recovery (33% by ALC; 18% by CD4 lymphocyte counts), radiation completion (23%), and chemotherapy completion (7%). Glucose-6-phosphate dehydrogenase levels were routinely checked by only 13% of respondents.

Conclusions. PJP prophylaxis is commonly used in HGG patients, but there are large variations in practice patterns, including the duration of prophylaxis. As consideration for PJP prophylaxis affects all patients with HGG, standardization of prophylaxis should be formally addressed.

Keywords
glioblastoma | glucose-6-phosphate dehydrogenase | high-grade glioma | lymphopenia | Pneumocystis carinii pneumonia | Pneumocystis jirovecii prophylaxis

High-grade gliomas are aggressive primary central neoplasms, graded as either anaplastic gliomas (World Health Organization [WHO] grade III) or glioblastoma (WHO grade IV), with glioblastoma being the most common and the most aggressive form with a less than 5% five-year survival rate with treatment. Even though high rates of recurrence and lack of efficacious treatment remain the primary challenge in the treatment of these cancers, it is
important to manage and prevent severe treatment-related complications. One of the most serious but preventable complications is Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia), which can be prevented by the use of PJP prophylaxis. Standard-of-care treatment for newly diagnosed high-grade gliomas is a combination of radiation, chemotherapy, and often steroid administration, which have all been shown to act as separate risk factors for development of PJP. Prophylaxis for this infection is generally recommended, but there is no clear consensus on the timing of initiation, maintenance, nor criteria for discontinuation. In this study we aim to capture current practice patterns and perceptions of the role of PJP prophylaxis in high-grade glioma patients from expert practitioners at National Cancer Institute (NCI)-designated cancer centers in the United States (US).

Materials and Methods

Survey

An online anonymous electronic survey of 14 questions was distributed to neuro-oncology experts at all NCI-designated cancer centers in the US. The survey was approved by the Johns Hopkins Institutional Review Board and disseminated via Survey Monkey (Palo Alto, CA) between May and June 2017. One reminder was sent to survey recipients who had not responded to the first request. The email addresses were obtained manually by surveying NCI-designated cancer centers’ websites, specifically searching for neuro-oncologists or medical oncologists who were treating patients with gliomas. Neurosurgeons, radiation oncologists, pathologists, neuro-radiologists, and advanced practice providers (nurse practitioners and physician assistants) were excluded. Demographic data including sex, training background (neuro-oncologist, medical oncologist, pediatric oncologist, pediatric neuro-oncologist), and the number of newly diagnosed high-grade glioma patients treated in the past year (1 to 10, 11 to 30, more than 31) were collected.

Surveyed patterns of practice included whether routine PJP prophylaxis was administered, at what time points during treatment, how and with what frequency lymphopenia was monitored, choice of first- and second-line prophylactic agents, whether the provider routinely monitored for glucose-6-phosphate dehydrogenase (G6PD) deficiency, and prophylaxis discontinuation criteria.

Statistical Considerations

The general survey questions were multiple choice or binary outcome. The overall survey response rate was defined as the number of survey responses received out of the total surveys sent to all potential participants. All source data were kept in an Excel file. The individual survey question data were summarized as a proportion, with the total number of respondents as the denominator. All results are considered descriptive and represent the responses collected in this survey.

Results

Demographic Data

A total of 207 surveys were sent out, with 61 invitees responding in full, accounting for a response rate of 29%. Sixty-eight percent of responders were men, and 32% were women. By training, 72% were neuro-oncologists, 18% were medical oncologists, and 10% were pediatric oncologists or neuro-oncologists. Almost half of them (49%) have practiced for more than 10 years after fellowship, 26% 5 to 10 years, and 25% less than 5 years. The majority of the participants (59%) have treated more than 31 patients with newly diagnosed high-grade gliomas within the last year, while 31% treated between 11 and 30 patients, and 10% have treated 1 to 10 patients within the last year.

Practice Patterns

The majority of the respondents routinely prescribe PJP prophylaxis (70%), while a minority (7%) do not. Multiple answers were allowed for PJP prophylaxis indication: based on lymphocyte/CD4+ count (67%), during radiation therapy (46%), and during adjuvant chemotherapy (26%). While 12% of participants reported not monitoring for lymphopenia, the majority of respondents reported using the absolute lymphocyte count (81%), and a smaller percentage (13%) CD4+ lymphocyte counts for lymphopenia monitoring. As for the frequency of monitoring, 42% of respondents stated that they monitor on a monthly basis, 26% weekly, and 14% every 2 weeks. The vast majority of respondents reported using trimethoprim-sulfamethoxazole (TMP-SMX) as the first-line agent for prophylaxis (88%), followed by pentamidine (6%) (Fig. 1A). Preference of second-line agents was more variable with dapsone chosen by most providers (Fig. 1B). Only 13% of respondents stated that they routinely check for G6PD levels. In our survey, there was no consensus on an appropriate time point for discontinuation of PJP prophylaxis. While 50% of respondents discontinue prophylaxis based on improvement or normalization of lymphocyte counts, 30% stated that they treat until the end of radiation therapy or the end of chemotherapy (Fig. 2). Nineteen percent did not further specify their practice pattern regarding discontinuation of PJP prophylaxis.

Discussion

The relationship between Pneumocystis pneumonia and HIV-induced immunosuppression was noticed early into the AIDS epidemic, and first evidence on safety and efficacy subsequently emerged for prophylaxis. Today, cancer-induced immunosuppression, treatment-related lymphopenia in adults and children, different chemotherapy regimens, radiation therapy, and glucocorticoid administration are known risk factors for Pneumocystis pneumonia. Without PJP prophylaxis, there
is an increased risk of *Pneumocystis* pneumonia among brain tumor patients with an incidence of about 1%, associated with a mortality rate of more than 50%. It was found to be related to all therapeutic modalities including steroids, temozolomide, as well as radiation. The first systematic review with meta-analysis of randomized, controlled trials on PJP prophylaxis in non-HIV–infected patients recommends starting prophylaxis if the risk for PJP is higher than 3.5%. A Cochrane systematic review of literature on PJP prophylaxis in non-HIV–immunocompromised patients was performed in 2014. It concluded that prophylaxis with TMP-SMX led to a decrease in PJP-related mortality, with a number needed to treat of 19. However, the subpopulation of patients with solid malignancies had a relatively low incidence of PJP, therefore the authors recommended prophylaxis only in patients with primary or metastatic brain tumors receiving a glucocorticoid, with TMP-SMX 3 times per week. A systematic review performed by De Vos et al in 2013 recommended initiation of PJP prophylaxis in high-grade glioma once lymphocyte count falls below 500 cells per μL or CD4+ count falls below 200 cells per μL, and continuing it until temozolomide had been stopped and CD4+ count is above 200 cells per μL. A group of experts from Australia created a guideline for diagnosis, prophylaxis, and management of PJP in patients with hematologic and solid malignancies. They recommend prophylaxis in patients with solid malignancies who are receiving steroids, as well as in all patients with brain tumors, especially if temozolomide or craniospinal irradiation is planned. The National Comprehensive Cancer Network (NCCN) recommends PJP prophylaxis in patients receiving prednisone equivalent of 20 mg or more daily for 4 or more weeks, and with concomitant use of temozolomide and radiation therapy until recovery from lymphopenia is achieved. Additionally, the prescribing information for temozolomide includes a warning statement regarding PJP risk and dictates that prophylaxis is required for all patients receiving concomitant temozolomide and radiotherapy for the 42-day regimen. Still, some authors recommend against PJP prophylaxis during treatment.
with temozolomide citing their center’s experience with low incidence, which does not justify potential side effects of prophylactic antibiotics.23

There are several agents with proven efficacy against PJP, including TMP-SMX, atovaquone, aerosolized or intravenous pentamidine, and dapsone. Currently no trials on efficacy of prophylaxis in patients with CNS tumors exist, and evidence is drawn either from the HIV-infected population,24-27 or the non-HIV–infected patient populations consisting primarily of solid organ transplant recipients and those with hematologic malignancies.18 Among choices for prophylaxis NCCN prefers TMP-SMX because of the large body of evidence for its efficacy, as well as additional benefit against other pathogens including Nocardia, Toxoplasma, and Listeria. For TMP-SMX–intolerant patients, second choices include desensitization to TMP-SMX, and other aforementioned agents. Even though pentamidine and atovaquone offer a better side effects profile than TMP-SMX, predominantly myelosuppression and rash as well as methemoglobinemia in G6PD-deficient patients, their disadvantages include higher costs and less efficacy.29,30

Inhaled pentamidine requires administration in negative-pressure rooms to minimize exposure of health care workers. However, as it requires only monthly supervised administration in the clinic, it may be a preferred option for noncompliant patients. Dapsone, even though efficacious, is a notorious cause of methemoglobinemia in G6PD-deficient patients, with one retrospective case series citing it as its cause in 42% of patients.33 Even though more common in areas with endemic malaria, G6PD deficiency was noted in 2.5% of males and 1.6% of females in the US army, African American men and women (12.2% and 4.1%, respectively) having the highest prevalence,34 and it can be expected that the numbers will be changing over time with increasing diversity of the population in the US. For treatment of methemoglobinemia, discontinuation of the offending agent is recommended, followed by intravenous methylene blue if patients are symptomatic and/or in cases of high methemoglobin levels.33

In our study more than two-thirds of survey participants stated that they routinely administer PJP prophylaxis. The treatment indication was predominantly based on lymphocyte and/or CD4+ counts, active radiation therapy, and more rarely whether the patient was receiving adjuvant chemotherapy. More participants stated that they follow absolute lymphocyte counts rather than CD4+ lymphocyte counts. The reason for this was not assessed in this survey, but following total lymphocyte counts as a surrogate for CD4+ counts is supported in the literature as absolute lymphocyte counts have been found to be predictive of CD4+ counts in patients.35 As far as the primary choice of therapy, most of the respondents chose TMP-SMX. Answers were more equally distributed between second-line therapy agents. This can be understood in context of the literature, which offers only limited evidence on the superiority of secondary agents in non-HIV-infected patients. There was notable variability in duration of PJP prophylaxis and parameters that are chosen to determine the time point for discontinuation of prophylaxis. Interestingly, only a minority of participants stated that they routinely screen for G6PD deficiency.

Our study had several limitations. These include a low sample size and a relatively low response rate of 29%. In
addition, there was potential selection bias in patterns of PJP prophylaxis considering that only physicians practicing at NCI-designated cancer centers were selected for this survey. Thus, these results might not correlate with the general patterns of practice.

As all patients with high-grade gliomas who are undergoing standard-of-care treatment receive immunosuppressive therapy with radiation, chemotherapy, and often steroids, a more standardized approach regarding PJP prophylaxis should be developed. Finding consensus not only on antibiotics for PJP prophylaxis but also on the duration of therapy may help to provide appropriate protection for a larger number of patients. In addition to providing more streamlined clinical practice patterns within standard of care, further harmonization of PJP prophylaxis may also standardize the care of patients in clinical research protocols. Given the paucity of data on ideal PJP prophylaxis in patients with malignant gliomas, it appears reasonable to presently recognize and follow the practice pattern of prophylaxis in patients with HIV, for whom distinct guidelines are already available.

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