

Pneumocystis Pneumonia and Acute Myeloid Leukemia: A Systematic Review

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Abstract

Abstract: Background: Pneumocystis pneumonia (PCP) incidence in acute myeloid leukemia (AML) patients have not been well described and some studies have shown the risk of this infection in these groups of patients. In this systematic review, we reviewed the published studies about PCP in AML to evaluate the PCP incidence and outcomes in these patients and then focuses on its immunological mechanism. Method: All articles reviewed in this collection are from recruited sites: PubMed and Embase databases. No time limit was considered for article searching. The following keywords were used: (“Pneumonia, Pneumocystis” OR Pneumocystis Pneumonia” OR “Pneumocystis jirovecii”), AND (“leukemia, myeloid, acute OR acute myeloid leukemia”). Our search strategy yielded 356 articles. After implementing the exclusion and inclusion criteria, the final papers were selected and reviewed. Result: By our search, 356 articles were found (316 in PubMed and 40 in Embase). After the implementation of inclusion and exclusion criteria, seven papers remained. A total of seven articles with a total number of 41 patients were included. Conclusion: Affected patients appear to have a clear resistance to PCP infection despite chemotherapy and bone marrow suppression due to the preservation of a specific immunological milieu in the lung. In fact, may be due to immunological stability of the lungs that remains intact. Further studies are needed.

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Review criteria: how did you gather, select and analyze the information you considered in your review?

We have searched all of the databases and literature associated with this topic in Pubmed, Google Scholar, EMBASE databases. Then, We proceed regard to PRISMA flowchart. In this review, there have been identified 356 articles.

Message for the clinic: what is the ‘take-home’ message for the clinician?

the aim of this study was to evaluate what is the probability of PCP infection and acute myeloid leukemia and then evaluate why this probability is low in this certain population. So this is always an important question for us that how the difference between myeloid leukemia and lymphoid leukemia would be justified.

Keywords: Acute myeloid leukemia, pneumocystis pneumonia, pneumonia, pneumocystis jirovecii, pneumocystis, systematic review

Pneumocystis pneumonia and acute myeloid leukemia: a systematic review

Introduction

There are several important issues about patients with immunosuppression especially patients with malignancy. One of the most important of them is the higher risk of opportunistic infections which are common among them especially in patients with hematologic malignancies, who have received intensified chemotherapeutic regimens [1, 2]. As we see in literature there are many aspects that may be questionable during routine clinical practice and some of them would change according to new findings in clinical guidelines. The major aim of prescribing prophylactic antimicrobial therapy is to reduce the infection related morbidity and mortality [3] and the overwhelming possible infections related complications which may reduce the treatment tolerability, so use of prophylactic antimicrobials were introduced from long time ago and that was widely studied [4, 5]. However these agents are not absolutely without adverse effects.

Pneumocystis jirovecii, is an atypical fungus that transmits via airborne route in respiratory droplets. This agent is in dormitory state in immunocompetent hosts, and can transmit to others within sufficiently close distance [6]. It remains asymptomatic as long as the host would be immunocompetent [7]. Once the host becomes immunocompromised, the organism becomes activated and proliferated [8].

This agent has several components in its cell wall. The main component is β -1,3-glucan [9, 10]. The first interaction is between macrophage receptor dectin-1 and β -1,3-glucan [11, 12]. This interaction leads to activation of lung macrophages and then releasing of several pro-inflammatory cytokines such as Tumor necrosis factor α (TNF α), Interleukin 8 (IL-8) [13-15]. This pro-inflammatory state results in neutrophil and other inflammatory cells recruitment, which is correlated directly to the lung inflammation, acute respiratory failure [11, 16]. Patients with malignancy or immunodeficiency who have impaired in innate immune system function, cannot clear the fungi and are predispose to Pneumocystis jirovecii pneumonia (PCP). Also TNF blockade results in lack of immune response to Pneumocystis [17]. In addition to innate immunity, lymphocytes especially CD4⁺ and CD8⁺ play a major role in host defense against pneumocystis jirovecii. TNF, IL-1 and IL-8 directly stimulate T lymphocyte recruitment and activation [18, 19].

There are several risk factors that predispose people to developing PCP. The main factor is impaired cell mediated immunity, which has the essential role in defending against fungi. When CD4 counts drop below the 200 cells/mm as in HIV patients, Pneumocystis prophylaxis warranted. Other causes of predisposition are solid organ transplant especially renal, heart and lung transplant recipients [20, 21]. In patients with hematological or oncological malignancies who receive chemotherapeutic regimens and become neutropenic, Pneumocystis infection is likely. Also in patients receiving corticosteroid more than 15-25 mg Prednisolone or more than 4 mg Dexamethasone daily for more than 4 weeks are at higher risk of developing infection [22, 23]. These amounts of corticosteroid use are seen in chemotherapeutic regimens especially in lymphoblastic leukemia or some chemotherapeutic regimens of lymphoma. Higher dose of corticosteroid (more than 60 mg daily) or concomitant use of Cyclophosphamide would have an additional risk in developing Pneumocystis infection [24]. Alemtuzumab that causes T cell depletion predisposes to Pneumocystis infection. Other chemotherapeutic regimens such as FCR (Fludarabine, Cyclophosphamide, and Rituximab), ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine), R-CHOP (Rituximab, Cyclophosphamide, Adriamycin,

Vincristine, and Prednisolone) in 14 days, also input patients into higher risk of Pneumocystis infection [25-28]. The risk of developing Pneumocystis infection in oncological malignancies are much lower than in hematological ones, so routine prescription of Pneumocystis prophylaxis are not recommended. In patients with brain tumors especially who receive an alkylating agent, Temozolamide as in patients with high grade gliomas, concurrent use of radiation therapy and also corticosteroid may increase the risk of infection [29]. Finally in patients with solid tumor who receive more than 20 mg Prednisolone or equivalents for more than four weeks are at increased risk for Pneumocystis infection, so routine prophylaxis is recommended [30]. Restoration of CD4 counts with highly active antiretroviral therapy (HAART) in HIV patients or passing of nadir phase in patients receiving chemotherapy, leads to decrease the risk of developing infection [31].

In hematologic malignancies, risk of developing PCP depends strongly on the underlying disorders. Patients with AML have much lower risk of Pneumocystis infection and up to now there is no recommendation for prophylactic use of antimicrobials for Pneumocystis in these patients. Due to limited information about the PCP incidence in AML patients, this review assess data on PCP incidence and outcome in AML.

Method

This review conforms to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement [32].

Search strategy

PubMed and Embase databases were searched to retrieve relevant English language articles. Keywords for search strategy were as follows: ("Pneumonia, Pneumocystis" OR Pneumocystis Pneumonia" OR "Pneumocystis jirovecii"), AND ("leukemia, myeloid, acute OR acute myeloid leukemia").

Screening process and study selection

There were no restrictions on the article's publication date, but only studies written in English were selected. Searchers were performed by one of the authors. All potentially English relevant articles retrieved from each database were screened. Two reviewers independently reviewed titles and abstracts and chose articles fitting selection criteria for full-text evaluation. Discrepancies were discussed with a third reviewer. Irrelevant articles were excluded. Based on inclusion and exclusion criteria and full-text assessment, eligible studies were identified. Then the content was analyzed, and data were extracted (Figure 1).

Criteria for considering studies for this review

There were no restrictions on the article's publication date. We evaluated all case reports, case series and observational studies that were about the prevalence of PCP in patients with AML. Studies with relevant information were included in the final analysis. Titles, abstracts, and full texts of the recorded studies were evaluated based on the inclusion and exclusion criteria. The inclusion criteria were as follows: 1) studies including clinical trials, observational studies, case reports, case series and case letters on PCP and AML. We select papers with no date restriction which evaluated incidence of PCP in AML patients, clinical manifestations, chemotherapy regimen, phase of treatment and also outcome; 2) availability to the full-text articles; 3) only English language articles. Studies with at least one of the following aspects were excluded: 1) studies with non-relevant information, 2) studies with language other than English, 3) review articles and letters, 4) duplicate studies and 5) articles available only in abstract form. Appropriate papers were selected after evaluating all studies based on the inclusion and exclusion criteria.

Data extraction

The following data were extracted from the research included: authors, year of study, study type, number of patients, age, gender, chemotherapy regimen, phase of treatment and patient outcome. To abstract the papers, two authors evaluated different parts of the articles to ensure the relevance of the subject to the research objectives. Results of data classification were reviewed by one of the authors. In terms of article inclusion, if any disagreement existed between the two reviewers, another member of our research team was contacted to resolve any discrepancies.

Results:

As shown in Figure 1, a total of 356 studies were identified from databases (316 in PubMed and 40 in Embase) and after deleting duplicates, 333 articles were reviewed based on the title and abstract. Of these, 311 articles were excluded, and 22 entered the next step. Then, the studies were reviewed based on the full-text and inclusion and exclusion criteria, and finally, seven papers were included in the study. Studies, classified into four case reports, two retrospective and one prospective study including totally 41 cases. Systematic review of cases with PCP in patients with AML are summarized in table 1 and 2. Table 1 shows the characteristics of patients with AML and PCP and table 2 shows the chemotherapy regimen, phase of treatment and outcomes [2, 33-38].

Discussion:

Based on studies and guidelines, lymphoproliferative disorders, acute and chronic lymphocytic leukemia and multiple myeloma constitute the vast majority of PCP cases in hematologic patients and PCP prophylaxis recommend in them [39, 40]. Based on guidelines, PCP in acute myeloid leukemia and myelodysplastic syndromes are rare and sparse and routine prophylaxis in these settings are not recommended. The reason for this recommendation maybe that PCP as fungi interacts with lymphocytes and in these myeloid disorders, the main abnormality is in myeloid precursors [26, 41, 42]. Another explanation is that steroids are used in chemotherapeutic regimens in lymphoproliferative disorders, lymphocytic leukemia and also multiple myeloma and this agent beside anti CD20 antibodies have no role in induction or consolidation therapy in myeloid disorders. The guidelines up to now recommend prophylaxis for Cytarabine only in lymphoproliferative disorders [43]. Unlike adults, in pediatric AML, routine prophylaxis for PCP is recommended [44].

Some studies focuses on the PCP incidence in AML patients. In a study conducted in Taiwan in 2018, 291 patients with AML were analyzed. 14 patients had definitive PCP and 6 patients had possible PCP. They found that there was an incidence of 6.8% risk of developing PCP in AML and 2% risk for each cycle of chemotherapy they received and the authors concluded that, prophylaxis should be considered in AML [33]. In contrast, Antoine R et al. in 2015, illustrated about two studies conducted in 1990-1999 and 2014 that among 55 and 321 patients with PCP, only 8 and 9 patients had AML respectively. The authors concluded that the diagnosis of PCP should not be part of the initial diagnostic process or therapy in patients with AML and the prophylaxis is not recommended [34, 45]. Some sparse case reports infavor of acute myeloid leukemia and PCP are available. In 2000, the authors presented a 30 year-old man with AML treated with subcutaneous low dose cytarabine. After one week he had signs and symptoms of sweet syndrome and PCP, with bilateral lung infiltration [37]. Lemez et al. treated 51 patients with AML and 3 patients with Myelodysplastic syndromes with Daunorubicin and Cytarabine. They received TMP-SMX for prophylaxis of pneumocystis. Only one of the eighteen patients without TMP-SMX prophylaxis during the first course of chemotherapy developed PCP that was treated with intravenous TMP-SMX [46]. An agent named Gemtuzumab ozogamicin is an anti CD33 monoclonal antibody which was approved for treatment of CD33+ AML in induction and consolidation therapy. CD33 is expressed on monocytes, granulocytes and myeloid progenitors and CD33 targeted therapies lead to myeloid cells depletion [47]. In results of reported trials for administering Gemtuzumab in AML patients, there was no increase in risk of infection due to this agent [47, 48].

Cytarabine which is the backbone of chemotherapy in myeloid disorders has an association with increased risk of PCP. Also it has been shown that T lymphoblasts are more active as compared to myeloblasts in cellular transport of cytarabine and this suggests that this agent is not only myelotoxic but is also profoundly immunosuppressive. Despite recovery of neutropenia, lymphopenia due to prolonged effect of cytarabine may make the patient susceptible to PCP.

We should also focuses on the role of alveolar macrophages. Macrophages are the front line of the anti-microbial defenses in the lung alveolar cavities. The major function of this cell and one of their most important roles is to fight against organisms and clean them across the alveolar cavities. Among these agents,

Pneumocystis spp. are more sensitive to its killing functions. The most important biological manifestation of these cells is their ability to regenerate in this space. This makes them permanently present in this structure, so called self-renewing system. Given that they have tissue establishment at the beginning of the embryonic stages called: embryonic prenatal development. Therefore, they are present in the lungs under any circumstances. It is one of the cases that despite performing chemotherapy and bone marrow suppression during the treatment of AML patients, no serious damage is done to the above function and capability. Especially in the case of monoclonal antibodies therapies that, despite their positive effect on myeloid suppression in the bone marrow, are not able to eliminate alveolar macrophages because they have very low expression of CD33 surface marker. It can be concluded that in this malignancy, and during treatment, there is minimal damage to the function of these cells in killing *Pneumocystis spp.* and the need for less prophylactic antibiotic. Further studies can help and determine the true risk of PCP in patients with AML.

Conclusion:

The main point is that there are several patients with PCP belonging to categories not generally recommended to be treated with prophylactic cotrimoxazole and one of these categories are AML patients. Data in literature are so limited and sparse in association of pneumocystis in patients with AML. It seems that affected patients appear to have a clear resistance to PCP infection despite chemotherapy and bone marrow suppression due to the preservation of a specific immunological milieu in the lung. In fact, may be due to immunological stability of the lungs that remains intact. Further studies can determine the risk of PCP in patients with AML.

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Figure 1. Flow chart of study selection for inclusion in the systematic review.

Table 1 . Characteristic of included studies.

Year	References	Age/ mean age	Gender	No. of patients	Type of study
2018	Chang et al. (33)	55.5	14 Male 6 Female	20/291	Retrospective
2002	Pagano et al. (2)	-	-	8/55	Retrospective
2014	Roux et al. (34)	-	-	9/544	Prospective
1997	Otsuka et al. (35)	33	Female	1	Case report
1998	Ong et al. (36)	28	Male	1	Case report
2000	Chowdhary et al. (37)	30	Male	1	Case report
2001	Theron et al. (38)	21	Male	1	Case report

Table 2. Chemotherapy regimen, phase of treatment and outcomes.

Year	No. of patients/ Phase of treatment	No of patients/ Chemotherapy	Outcome
2018	11/ Complete remission 4/ Refractory 3/ Relapse 2/ New diagnosis	10/ HDAC 3/ FLAG 2/ D 1/ EMA 1/ C 1/ E, C 1/ 7+ 3 1/ None	6/ Deceased 14/ Cure
2002	2/ Induction, Re-induction 1/ Consolidation 1/ Maintenance 1/ Salvage	Not determined.	Not determined.
2014	9/ Consolidation	Not determined.	Not determined.

Year	No. of patients/ Phase of treatment	No of patients/ Chemotherapy	Outcome
1997	Complete remission	Daunorubicin, Cytarabine, 6-Mercaptopurine	Cure
1998	Complete remission	EMA	Cure
2000	Complete remission	Cytarabine	Deceased
2001	Post consolidation	Daunorubicin, Cytarabine, Etoposide	Cure

C, cytarabine; D, daunomycin; HDAC, high dose cytarabine; FLAG, fludarabine, cytarabine and granulocyte-stimulating factor; 7+3, idarubicin (3 days) + cytarabine (7 days); EMA, Mitoxantrone, Cytarabine Etoposide; E, etoposide.

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