Single-Day Trimethoprim/Sulfamethoxazole Prophylaxis for *Pneumocystis* Pneumonia in Children with Cancer☆

Désirée Caselli, MD[1,*], Maria Grazia Petris, MD[2], Roberto Rondelli, MD[3], Francesca Carraro, MD[4], Antonella Colombini, MD[5], Paola Muggeo, MD[6], Ottavio Ziino, MD[7], Fraia Melchionda, MD[3], Giovanna Russo, MD[8], Paolo Pierani, MD[9], Elena Soncini, MD[10], Raffaella DeSantis, MD[11], Giulio Zanazzo, MD[12], Angelica Barone, MD[13], Simone Cesaro, MD[14], Monica Cellini, MD[15], Rossella Mura, MD[16], Giuseppe M. Milano, MD[17,**], Cristina Meazza, MD[18], Maria P. Cicalese, MD[19], Serena Tropia, MD[7], Salvatore De Masi, MD[20], Elio Castagnola, MD[21], and Maurizio Aricò, MD[1,***], on behalf of the Infectious Diseases Working Group of the Associazione Italiana Ematologia Oncologia Pediatrica[****]

Objective To determine whether a simplified, 1-day/week regimen of trimethoprim/sulfamethoxazole is sufficient to prevent *Pneumocystis* (*jirovecii* [*carinii*]) pneumonia (PCP). Current recommended regimens for prophylaxis against PCP range from daily administration to 3 consecutive days per week dosing.

Study design A prospective survey of the regimens adopted for the PCP prophylaxis in all patients treated for childhood cancer at pediatric hematology-oncology centers of the Associazione Italiana Ematologia Oncologia Pediatrica.

Results The 20 centers participating in the study reported a total of 2466 patients, including 1093 with solid tumor and 1373 with leukemia/lymphoma (or primary immunodeficiency; n = 2). Of these patients, 1371 (55.6%) received the 3-day/week prophylaxis regimen, 406 (16.5%) received the 2-day/week regimen, and 689 (27.9%), including 439 with leukemia/lymphoma, received the 1-day/week regimen. Overall, only 2 cases of PCP (0.08%) were reported, both in the 2-day/week group. By intention to treat, the cumulative incidence of PCP at 3 years was 0.09% overall (95% CI, 0.00-0.40%) and 0.51% for the 2-day/week group (95% CI, 0.10%-2.00%). Remarkably, both patients who failed had withdrawn from prophylaxis.

Conclusion A single-day course of prophylaxis with trimethoprim/sulfamethoxazole may be sufficient to prevent PCP in children with cancer undergoing intensive chemotherapy regimens. This simplified strategy might have implications for the emerging need for PCP prophylaxis in other patients subjected to the increased use of biological and nonbiological agents that induce higher levels of immune suppression, such as those with rheumatic diseases. *(J Pediatr 2014;164:389-92)*.

Pneumocystis (*jirovecii* [*carinii*]) pneumonia (PCP) is an opportunistic infection first recognized by the middle of the 20th century. Its incidence has increased over the last several decades, owing to the wider use of immunosuppressive therapy in organ transplant recipients and in patients with cancer or congenital or acquired severe immune deficiency.[1-3] Before the use of prophylaxis, up to 43% of children with cancer developed PCP.[4] It is known that asymptomatic or mild pulmonary infections, defined as colonization, are widely observed in the general adult population. Serologic studies have shown that primary *P jirovecii* infection (as defined by the development of antibody responses to antigens) is acquired in early childhood; 70%-90% of healthy children exhibit serum antibodies to the organism by age 2-3 years.[5]

Genetic and epidemiologic data on *P jirovecii* infections in Italy are scarce, limited to defined geographical regions and mainly regarding isolates from patients with HIV infection. Dimonte et al[6] investigated a cohort comprising 263 patients from

AIEOP	Associazione Italiana Ematologia Oncologia Pediatrica
PCP	*Pneumocystis* (*jirovecii* [*carinii*]) pneumonia
SMX	Sulfamethoxazole
TMP	Trimethoprim

From the [1]Department of Pediatric Hematology-Oncology, Azienda Ospedaliero Universitaria Meyer Children Hospital, Florence, Italy; [2]Pediatric Hematology-Oncology, Padua, Italy; [3]Pediatric Oncology and Hematology, Lalla Seràgnoli Unit, University of Bologna, Bologna, Italy; [4]Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, Turin, Italy; [5]Pediatric Hematology-Oncology, Monza, Italy; [6]Pediatric Hematology-Oncology, Bari, Italy; [7]Pediatric Hematology-Oncology, ARNAS Civico, Palermo, Italy; [8]Pediatric Hematology-Oncology, Catania, Italy; [9]Division of Pediatric Hematology/Oncology, G Salesi Women's and Children's Hospital, Ancona, Italy; [10]Pediatric Hematology-Oncology, BMT Unit, Spedali Civili, Brescia, Italy; [11]Pediatric Hematology-Oncology, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [12]Pediatric Hematology-Oncology, Institute for Maternal and Child Health - IRCCS Burlo Garofolo, Trieste, Italy; [13]Pediatric and Hematology-Oncology, University Hospital Azienda Ospedaliero Universitaria di Parma, Parma, Italy; [14]Pediatric Hematology-Oncology, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; [15]Pediatric Hematology-Oncology, University Hospital, Azienda Ospedaliero Universitaria Policlinico, Modena, Italy; [16]Pediatric Hematology-Oncology, Cagliari, Italy; [17]Pediatric Oncology/Hematology, BMT Unit, Section of Hematology, Department of Internal and Experimental Medicine, University of Perugia, Perugia, Italy; [18]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionaledei Tumori, Milan, Italy; [19]Pediatric Immunology, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy; [20]Epidemiology, Azienda Ospedaliero Universitaria Meyer Children Hospital, Florence, Italy; and [21]Infectious Disease Unit, Gaslini Institute, Istituto Giannina Gaslini, Genoa, Italy.

*Current affiliation: Dept. Medical Direction, Azienda Ospedaliero Universitaria Meyer Children Hospital, Florence, Italy.

**Department of Pediatric Hematology/Oncology, Ospedale Pediatrico Bambino Gesù, Rome, Italy.

***Pediatric Hematology Oncology Network, Istituto Toscano Tumori , Florence, Italy.

****A list of members of the Infectious Diseases Working Group of the Associazione Italiana Ematologia Oncologia Pediatrica is available at www.jpeds.com (**Appendix**).

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2 major hospitals; 38 immunocompromised patients, including 25 patients with HIV infection; and 225 immunocompetent patients by polymerase chain reaction amplification of the mtLSU-rRNA gene and found that 25.5% were positive.

More than 40 years ago, Hughes et al[4] documented successful prophylaxis with daily trimethoprim (TMP)/sulfamethoxazole (SMX) in pediatric oncology patients. At present, this procedure is considered the standard of care for children with an immune defect due to chemotherapy or prolonged corticosteroid therapy.[7-9] The finding of the efficacy of daily, but intermittent prophylactic dosing of TMP/SMX was recognized in numerous subsequent studies.[7-12]

Current recommendations for TMP/SMX dosing for PCP prophylaxis in immunocompromised patients are based on either daily or 3 consecutive days per week dosing.[4,12] A recent study reported intermittent dosing of TMP/SMX based on a regimen of 2 consecutive days per week, used routinely for PCP prophylaxis in pediatric patients with leukemia and lymphoma. This dosing regimen was derived from studies on bone marrow transplantation recipients.[10]

The aim of the present study was to assess whether a less-intensive, 1-day/week regimen is sufficient to prevent PCP. To explore this issue, we performed a prospective survey of the results of PCP prophylaxis in children treated at pediatric hematology-oncology centers of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP).

Methods

All of the AIEOP centers were invited to participate in this prospective survey of PCP prophylaxis. Only patients with newly diagnosed cancer in 2009-2011 requiring chemotherapy and for which PCP prophylaxis was considered indicated according to local policy were eligible for the study.

Data on the total number of patients treated in study years, the number of solid tumors vs leukemia/lymphoma, criteria for prescribing PCP prophylaxis, the schedule of prophylactic regimens, and the number of cases of PCP reported prospectively in this cohort were collected. Data were collected as part of the supportive therapy in the individual disease-related protocol, with the informed consent of the patients' legal guardians. The capture of all PCP cases was performed by each participating center by using individual patient records, local databases, and study-specific data collection forms.

The data were collected on a specific form and pooled. The cumulative incidence of PCP was calculated both overall and in the 3 subgroups defined by duration of PCP prophylaxis. The differences in the cumulative incidence among subgroups were calculated using the Gray test. The analysis was performed on an intention-to-treat basis. The main presenting features (sex and age), the type of cancer diagnosis (hematologic malignancy vs solid tumor) were compared in the different therapeutic groups.

Results

A total of 20 centers participated in the study by reporting data on all of their patients newly diagnosed and treated between 2009 and 2011. These centers reported 3 different dosing regimens for PCP prophylaxis. Eleven centers prescribed a 3-day/week prophylaxis regimen, with TMP 5 mg/kg/day divided into 2 doses (total dose, 15 mg/kg/week). Six centers used a 2-day/week regimen with TMP either 10 mg/kg/day divided into 2 doses in 2 centers (total dose, 20 mg/kg/week) or 5 mg/kg/day divided into 2 doses in 4 centers (total dose, 10 mg/kg/week). The remaining 3 centers used the 1-day/week regimen, including 1 center with TMP 10 mg/kg/day divided into 2 doses, 1 center with 5 mg/kg/day divided into 2 doses, and 1 center with a 2-day/week (5 mg/kg/day divided into 2 doses) regimen for solid tumors and a 1-day/week (10 mg/kg/day divided into 2 doses) regimen for leukemia/lymphoma (**Table**). PCP prophylaxis was prescribed during the entire chemotherapy program.

A total of 2466 patients were analyzed, including 1093 with a solid tumor, 1371 with leukemia/lymphoma, and 2 with primary immunodeficiency. Among these patients, 1371 (55.6%) received the 3-day/week prophylaxis, 406 (16.5%) received the 2-day/week regimen, and 689 (27.9%) received the 1-day/week regimen.

Overall, only 2 cases of PCP (0.08%) were reported from the participating centers (**Table**). Both were enrolled in the group of patients receiving 2-day/week prophylaxis. In both cases, the diagnosis of PCP was suspected based on the clinical and radiologic findings and supported by polymerase chain reaction of bronchial aspirate or nasopharyngeal swab. Both patients were hospitalized and treated with intravenous high-dose TMP/SMX, and subsequently recovered.

The cumulative incidence of PCP at 3 years was as follows: overall, 0.09% (95% CI, 0.00%-0.40%); 2 days/week prophylaxis, 0.51% (95% CI, 0.10%-2.00%). Comparisons of the cumulative incidence of PCP in the 3 groups were as follows: 1-day/week vs 2-day/week, $P = .074$ (Gray test); 2-day/week vs 3-day/week, $P = .012$; 1-day/week vs 3-day/week vs 2-day/week, $P = .002$.

Remarkably, both of the patients who failed prophylaxis (ie, developed PCP during the study period) were not receiving prophylaxis, 1 because of drug intolerance and the other because of nonadherence to PCP prophylaxis.

To exclude a favorable selection bias in the therapeutic groups, we compared the frequency of patients with leukemia/lymphoma, aged up to 14 years (ie, the characteristics of the 2 patients who failed) in the 1-day/week group and the 2-day/week and 3-days/week groups, and were found to be comparable for age and duration of follow-up (P not significant, t test). Furthermore, when patients with leukemia/lymphoma were subdivided by age subgroup and diagnosis, no difference in the incidence of PCP was observed (P not significant, Fisher exact test).

Discussion

Although PCP prophylaxis for pediatric hematology/oncology patients has become the standard of care, the optimal regimen and duration of therapy have not been defined. The cumulative incidence of PCP in the 20