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Prospective Randomized Comparison of Two Prophylactic Regimens with Trimethoprim–Sulfamethoxazole in Leukemic Children: a Two Year Study

MARIO R. ROSSI, PATRIZIO BANFI, MARIALUISA CAPPUCCILLI, VALENTINO CONTER, DANIELA DE POLI, GABRIELLA PIACENTINI, MARIA G. ZURLO and GIUSEPPE MASERA

Centro di Ematologia Pediatrica, Università di Milano, Ospedale di Monza, Italy

Abstract—*Between 1 July 1984 and 30 June 1986 all children treated for acute hematologic malignancy at our center were randomized to receive continuous (group A) or intermittent (3 days/week, group B) prophylaxis with trimethoprim–sulfamethoxazole (5–25 mg/kg/day/p.o.) against interstitial pneumonia with the aim of investigating if an intermittent regimen is as effective as and less toxic than a continuous regimen. The number of severe infections (group A, 17; group B, 21) and side-effects (group A, 30; group B, 34) was similar in the two groups, and compliance was also similar.*

We conclude therefore that neither regimen offers advantages over the other and the decision which to use should be based on cost (where regimen B has the advantage) and the children's and parents' preferences and compliance.

INTRODUCTION

SINCE 1977 when Hughes *et al.* [1] reported that trimethoprim–sulfamethoxazole (TMP-SMZ) was effective in preventing *Pneumocystitis carinii* (PC) pneumonia in susceptible children and perhaps also bacterial infections, a multitude of trials with this drug have been reported, all attempting to demonstrate reductions in the frequency of bacterial infections complicating granulocytopenia. The results of these trials have varied, and TMP-SMZ has been shown to be effective only as prophylaxis and therapy for PC pneumonia [2–9].

In our center, the number of cases of interstitial pneumonia in leukemic children started to rise in 1981 (5 in 1981, 13 in 1982, 11 in 1983) with a high mortality rate (10% and 36% of the patients with interstitial pneumonia died in 1982 and 1983, respectively). Although it was not possible to demonstrate the etiologic agent, the clinical and radiologic features were compatible with PC pneumonia. For these reasons, starting in January 1984 we gave prophylaxis (TMP-SMZ 5–25 mg/kg/day/p.o.) to all children on antiblastic treatment for the duration of this treatment regardless of circulating neutrophil count. We performed a preliminary analysis at 6 months that seemed to indicate a reduction in the number of cases and forms of pneumonia, but there was also a high incidence of side-effects, especially hematologic (37 of 80 children interrupted prophylaxis at least once for neutropenia and/or anemia during maintenance treatment of leukemia) [10]. In order to continue prophylaxis and in an attempt to reduce the toxicity we started a randomized study to compare two different prophylactic regimens with TMP-SMZ, one continuous and the other intermittent, based on Hughes' report of an animal experiment [11]. Our aim was to determine whether intermittent courses of TMP-SMZ are as effective as continuous doses in the prevention of interstitial pneumonia and less toxic.

PATIENTS AND METHODS

Between 1 July 1984 and 30 June 1986 all children treated at our center for acute hematologic malignancy at first diagnosis or in relapse were randomized to receive continuous or intermittent TMP-SMZ as prophylaxis against interstitial pneumonia. Allocation of patients to a prophylactic

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Correspondence and reprint requests to: Dr. Mario Renato Rossi, Centro di Ematologia Pediatrica, Ospedale di Monza, Via Donizetti 106, 20052 Monza, Italy.

group was done by a doctor who held a random selection book.

TMP-SMZ was given orally twice daily in the form of a syrup as follows: Regimen A: 2.5–12.5 mg/kg/12 h 7 days a week; Regimen B: the same daily schedule as in regimen A but on 3 days a week (Monday, Tuesday, Wednesday). The drug was administered for all the duration of antiblastic treatment starting from the first day of induction. After discharge the drug was given by the parents.

The drug could be suspended: (a) during intensive antiblastic therapy only for severe gastrointestinal effects, allergy or refusal of the children or parents (the drug was never suspended for cytopenias during this phase of chemotherapy); and (b) during antiblastic maintenance only if neutrophils were under 1000/mmc, hemoglobin was under 8 g/dl, platelets were under 80,000/mmc, or for severe gastrointestinal effects, allergy or refusal.

Particular attention was given to the regular and continuous administration of TMP-SMZ, and we insisted with the children and parents on the importance of this. In an attempt to improve the accuracy of therapy administration (antiblastic and antiinfective), all the children were given a diary with the daily therapy schedule.

We compared the two groups for side-effects, infections and compliance; statistical comparison was performed with the chi-square test.

Compliance was evaluated after 1 year by two doctors interviewing the parents on the basis of a questionnaire that considered in particular the regularity with which the drug was taken and the reasons for modifying times of drug administration and dosage.

The efficacy of prophylaxis was evaluated considering the number of episodes of pneumonia or severe infection with or without a demonstrable localization in each group.

RESULTS

Of the 97 patients randomized, seven were withdrawn from the study (four in group A and three in group B): three refused to take the drug, two died early during remission induction therapy, one was allergic to sulfonamides, and one moved to another city.

Of the 90 evaluable patients 44 were in group A and 46 in group B. The general characteristics of the patients are summarized in Table 1. Ten patients in group A and six in group B were in leukemic relapse. Seven patients in group A and 10 in group B had myeloid leukemia. The median duration of follow-up was 574 days (range 56–686) in group A and 615 days (range 53–686) in group B.

Infections

Seventeen infections were observed in group A as follows: fever of unknown origin (FUO) in 10 cases; bacteremia (both *E. coli*) in two; pneumonia in three; interstitial pneumonia in one; hepatic and splenic fungal abscess in one. All the infections occurred during intensive antiblastic therapy except two cases of pneumonia which developed during maintenance. The mean neutrophil count at infection onset was 260 ± 708 (S.D.)/mmc; the median duration of prophylaxis before first infection was 35 days (range 3–182). Seven out of 17 episodes (6/10 FUO and 1/1 interstitial pneumonias) occurred in patients with myeloid leukemia.

Of the 22 infections observed in group B 14 were FUO; two bacteremia (*E. coli* and *S. aureus*); three pneumonias; one meningitis; one enteritis; one interstitial pneumonia. One FUO, two pneumonias and the interstitial pneumonia occurred during maintenance treatment. The mean neutrophil count at the infection onset was 322 ± 931 (S.D.)/mmc. The median duration of prophylaxis before first infection was 23 days (range 1–180). Nine out of 22 infections (7/13 FUO, 1/2 bacteremias, and 1/3 pneumonias) occurred in patients with myeloid leukemia (Table 2).

A significant reduction in the number of pneumonias was noted in comparison with the years before the introduction of TMP-SMZ prophylaxis (Table 3).

Side-effects

Group A. During antiblastic maintenance therapy there were 18 suspensions of prophylaxis for granulocytopenia, seven for anemia and five for granulocytopenia associated with anemia; in addition three patients suspended the drug for gastrointestinal intolerance, three for refusal and one for allergy.

Group B. There were 26 suspensions for granulocytopenia, one for anemia, seven for granulocytopenia associated with anemia, six for gastrointestinal problems, and three for refusal. The number of episodes per patient ranged from 0 to 3 in group A and from 0 to 6 in group B.

The median duration of prophylaxis before suspension was 144 days (range 4–384 and 110 days (range 9–320) for groups A and B, respectively (Table 4).

Compliance

The data refer to only 1 year of follow-up. Forty-three patients were evaluable (20 in group A, 23 in group B); 3/20 of the children in group A and 5/18 in group B had some difficulties in taking the drug. The most common problems were drug refusal and

Table 1. General characteristics of the patients

	Regimen A Continuous	Regimen B 3 days/week
Patients	48	49
Evaluables	44	46
Age		
median	8 years	5 years 6 months
range	(11 months to 14 years)	(2 years 2 months to 15 years)
Acute lymphoblastic leukemia	27	30
Acute myeloid leukemia	7	10
Relapse	10	6
Follow-up		
median (days)	574	615
range	56–686	53–686

Table 2. Severe infections occurring during prophylaxis

	Regimen A Continuous	Regimen B 3 days/week
FUO	10	14
Bacteremias	2	2
Pneumonia	3	3
Interstitial pneumonia	1	1
Other	1	2
Total	17	22
Neutrophil count (mean) at onset of infection	260 ± 708 (S.D.)	322 ± 931 (S.D.)
Duration of prophylaxis before infection		
median	36 days	23 days
range	(3–182)	(1–180)

nausea. After a certain time, the knowledge that the drug had to be taken was sufficient to induce nausea, and refusal to take it followed automatically; these problems were overcome by various means (changing from syrup to tablets, changing the taste of the syrup, etc.). Although it had been feared that there would be difficulties in group B in remembering to take the drug as prescribed when the children were at home, this did not occur.

DISCUSSION

In the randomized trial we evaluated the efficacy and toxicity of two prophylactic regimens with TMP-SMZ (preliminary results were presented as a poster during the 4th International Symposium

Table 3. Severe infection occurring in children with leukemia by year

	1982		1983		1984		1985	
Neutrophils	<1000	>1000	<1000	>1000	<1000	>1000	<1000	>1000
Patients in therapy	109		114		115		114	
Infections	55	33	60	22	46	14	49	11
Bacteremia	10	0	12	0	7	0	7	1
FUO	20	4	27	2	29	2	32	2
Pneumonia*	9	14	13	12	4	2	2	4
Interstitial pneumonia**	5	8	3	8	0	3	2	2
Enteritis	1	0	3	0	2	0	0	0
Other	10	7	2	0	4	7	6	2

*Pneumonia episodes: 1982 vs. 1984 $P < 0.03$; 1982 vs. 1985 $P < 0.03$; 1983 vs. 1984 $P < 0.005$; 1983 vs. 1985 $P < 0.005$.

**Interstitial pneumonia: 1982 vs.1984 P = ns; 1982 vs. 1985 P = ns; 1983 vs. 1984 P = ns; 1983 vs.1985 P = ns.

Six of seven interstitial pneumonias recorded in 1984 and 1985 occurred in children who suspended prophylaxis.

Table 4. Episodes of side-effects occurring during prophylaxis causing suspension

	Regimen A Continuous	Regimen B 3 days/week
Neutrophils <1000/mmc	18*	26*
Hemolglobin <8 g/dl	7†	1†
Neutrophils + hemoglobin	5	7
Allergy	1	0
Bad compliance	3	3
Gastro-intestinal dysfunction	3	6
Total	37	43
Episodes by patient (range)	0–3	0–6
Duration of prophylaxis before suspension median (range)	144 (4–384)	110 (9–320)

*$P > 0.05$.
†$P < 0.025$.

on Infections in the Immunocompromised Host, Sweden 1986) [13]. Randomization was stopped after 2 years because of internal organization problems. Therefore, the data reported cannot be considered definitive and possibly a larger number of patients would have increased the power of the statistical tests. After a 2-year follow-up our data suggest that there are no significant differences between the two regimens as regards prophylactic efficacy and incidence of side-effects. The major benefit in both regimens was an important and significant reduction in the frequency of pneumonia. Neither of the two regimens showed a significant difference in the incidence of other severe infections.

From the point of view of side-effects, only two differences were observed between the two regimens. The incidence of granulocytopenia during maintenance treatment was inexplicably higher in group B but not significantly so, and the incidence of anemia was significantly higher ($P < 0.025$) in group A, which could be attributed to the antifolic activity of TMP-SMZ administered continuously.

As regards compliance, we found no differences between the groups, and it should be noted that although problems arose they were overcome by various means, and regular administration could be achieved in most cases. In conclusion, neither of the two regimens seems to offer substantial advantages over the other as prophylactic therapy, and the decision which to use should be based on cost (in which case regimen B has the advantage) and preferences shown by the children and parents.

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