Prophylaxis of Fever and Infection in Adult Cancer Patients

A Placebo-Controlled Trial of Oral Trimethoprim–Sulfamethoxazole Plus Erythromycin

BARNETT S. KRAMER, MD, DANIEL J. CARR, MD, KENNETH H. RAND, MD, PHILIP A. PIZZO, MD, ALICIA JOHNSON, BS, KATHLEEN J. ROBICHAUD, RN, AND JAMES B. YUCHA, MS

Oral trimethoprim–sulfamethoxazole (Bactrim) plus erythromycin (TMZ–E) was tested *versus* placebo (P) as prophylaxis for bacterial infection in a randomized, double-blind trial in adult cancer patients receiving cytotoxic chemotherapy expected to result in significant neutropenia. The incidence of adverse reactions attributable to TMZ and/or E was higher in drug-treated episodes (18 of 28 *vs* 3 of 29 for P, $P < 0.0005$) resulting in poorer compliance. The incidence of fever was not significantly different between episodes treated with TMZ–E (18/27) and those treated with P (17/29), nor was there a significant difference in the median interval between the onset of neutropenia and the onset of fever. However, 14 of 18 fevers in TMZ–E recipients were without a documented infectious source compared with only 6 of 17 in P recipients ($P < 0.05$). The same patterns were apparent even when episodes in which compliance with the regimen was either excellent or good were considered separately. There was no significant difference in the number of deaths from infection between TMZ–E and P recipients (3/27 *vs* 1/29). It is concluded that TMZ–E prophylaxis is of no practical benefit, may mask the cause of infection in febrile neutropenic cancer patients, and is associated with substantial toxicity.

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BACTERIAL INFECTION occurring during periods of neutropenia is a major life-threatening complication of cytotoxic chemotherapy in patients with cancer. The incidence and lethal nature of infection relates directly to the degree and duration of neutropenia induced.[1-4] The observation that most of these infections arise from aerobic gram-negative flora colonizing the alimentary tract has led to clinical trials using two types of prophylactic strategy. The first is nonselective gut sterilization with oral broad-spectrum nonabsorbable antibiotics. The second strategy is "selective" decontamination of aerobic gram-negative organisms with agents such as trimethoprim–sulfamethoxazole. The latter approach recognizes that anaerobes rarely cause infection in the neutropenic host,[2,5] and can help resist colonization by gram-negative aerobes.[6,7] Furthermore, when the two approaches were compared directly, trimethoprim–sulfamethoxazole was demonstrated to be equally effective, cheaper, and better tolerated than oral nonabsorbable antibiotics.[8-10]

Several investigators have reported that trimethoprim–sulfamethoxazole reduces fever and infection rates compared with controls, the benefits being most apparent in patients with prolonged, intense neutropenia,[11-13] and in patients with primary bone marrow disorders, rather than those with solid tumors undergoing cytoreductive treatment.[14] However, differences in study design, the concommitant use of other oral antibiotics in some trials[11,12] and the inclusion of some patients already infected at the start of prophylaxis[14] make it difficult to accept the use of prophylactic trimethoprim–sulfamethoxazole routinely in all neutropenic cancer patients. This agent was recently reported to be of no benefit in a population of adult leukemics undergoing consolidative therapy.[15] Though the drug is reportedly well tolerated in most cases, none of these investigations has prospectively assessed the role of patient compliance. The conflicting results, the need to monitor compliance and to assess further the efficacy of antibiotic prophylaxis in populations that in-

From the Divisions of Medical Oncology and Infectious Diseases, University of Florida College of Medicine, Gainesville, Florida, and the Infectious Disease Section, Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland.

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Address for reprints: Barnett S. Kramer, MD, Division of Medical Oncology, Box J-277, J. Hillis Miller Health Center, University of Florida, Gainesville, FL 32610.

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TABLE 1. Patient Characteristics

	Placebo	TMZ-E
Episodes	29	27
Patients	23	22
Sex (no. of episodes)		
Male	20	12
Female	9	15
Patient age each episode, median years (range)	60 (23–70)	51 (16–69)
Compliance* (no. of episodes)		
Excellent	21 } 26	13
		15
Good	5	2
Poor	2 } 3	5
		12
Protocol discontinued	1	7
Diagnosis† (no. of episodes)		
Solid tumor		
Chemotherapy only	16	5
Chemotherapy + marrow transplant	5	5
Total	21	10
Acute leukemia		
Initial induction	5	1
Reinduction	3	7
Consolidation	0	9
Total	8‡	17§

TMZ-E: oral trimethoprim–sulfamethoxazole (Bactrim) plus erythromycin.

* $\chi^2 = 6.643$, $P < 0.01$.

† Solid tumor *vs.* acute leukemia, $\chi^2 = 5.7217$, $P < 0.025$.

‡ Seven acute myeloblastic leukemia patients (AML) received daunorubricin plus cytosine arabinoside; one acute undifferentiated leukemia (AUL), vincristine plus prednisone.

§ Nine AMLs received daunorubicin plus cytosine arabinoside; two AMLs, cytosine arabinoside plus 6-thioguanine; two AMLs, daunorubicin/5-azacytidine/6-thioguanine; one AML, daunorubicin plus 5-azacytidine; one AML, m-AMSA; one acute lymphoblastic leukemia (ALL), daunorubicin plus L-asparaginase; one ALL, high-dose cytosine arabinoside.

clude solid tumor patients, combined with the theoretical risks in terms of acquisition of resistant organisms and allergic reactions, have made further trials mandatory.

Gram-positive cocci have become relatively more frequent pathogens in neutropenic hosts, accounting for a significant portion of serious infections in some centers.[5,16,17] Trimethoprim–sulfamethoxazole is reported to be generally effective against most of these pathogens[18]; however, we believed that the addition of an orally administered antibiotic with specific activity for gram-positive cocci might prove to be of benefit. Antibiotic sensitivity surveillance at our institution revealed that most gram-negative pathogens of importance in chemotherapy patients, excepting *Pseudomonas aeruginosa,* were trimethoprim–sulfamethoxazole-sensitive (94%–100% of isolates), and that isolates of *Staphylococcus aureus* were 100% sensitive to erythromycin. We therefore undertook a study of prophylactic trimethoprim–sulfamethoxazole (TMZ) (Bactrim) plus erythromycin stearate (TMZ-E) *versus* placebo (P) in adult cancer patients about to undergo chemotherapy expected to induce significant neutropenia.

Methods

This was a randomized double-blind study design performed concurrently with a trial conducted by Pizzo and associates in a pediatric cancer population at the National Cancer Institute, Bethesda, Maryland.[19] Patients receiving chemotherapy expected to result in neutropenia (defined as a blood count of bands plus segmented neutrophils 500/mm^3), and who gave informed consent, were considered eligible. The patients in this study were all adults on the Medical Oncology services of Shands Teaching Hospital and the affiliated Gainesville Veterans Administration Medical Center, in Florida. Patients were considered eligible regardless of tissue diagnosis, remission status, or specific chemotherapy regimen. Solid tumors were primarily small cell lung carcinomas treated with either high-dose CAV (cyclophosphamide 1200 mg/m^2, Adriamycin (doxorubicin) 70 mg/m^2, and vincristine 1 mg/m^2 intravenously (IV) every 3 weeks) or CAV-VP16, 213 (cyclophosphamide 1000 mg/m^2, Adriamycin 40 mg/m^2, vincristine 1 mg/m^2 day 1, plus VP-16-213 100 mg/m^2 days 1–3, every 3 weeks). There were a small number of patients with refractory solid tumors treated on a variety of high-dose regimens plus autologous marrow reinfusion. Patients with acute leukemia were treated as indexed in Table 1.

Patients entered onto protocol remained eligible for study re-entry during subsequent courses of chemotherapy but received the same prophylactic regimen (drugs or placebo) to which they were initially randomized. The only patients considered ineligible were those who were allergic by history to trimethoprim–sulfamethoxazole or erythromycin or who had developed a rash during a prior study entry, those who were already febrile or infected, those who had received any antibiotics in the preceding 72 hours, and those who declined to enter the study.

Patients randomized to receive TMZ–E were given doses based on body weight: 40.1 to 50 kg, E 625 mg twice daily + TMZ 200/1000 mg twice daily; 50.1 to 60 kg, E 750 mg twice daily + TMZ 240/1200 mg twice daily; 60.1 to 70 kg, E 875 mg twice daily + TMZ 280/1400 mg twice daily; >70 kg, E 1000 mg twice daily + TMZ 320/1600 mg twice daily. Doses were all administered in tablet form. Matched placebo tablets in an equivalent number and schedule were given to control patients. Occasionally patients received oral mycostatin prophylactically, depending on the primary physician's preference. Oral mycostatin was given prophylactically

during 5 courses of placebo and 8 courses of TMZ–E. No other antimicrobial agents were administered during the study period. No patients received granulocyte transfusions. Patients in whom prolonged marrow suppression was anticipated were hospitalized in private rooms with modified reverse isolation techniques (masks and hand washing) employed, whereas other patients were followed in the outpatient clinics. No patients were placed in laminar air flow environments.

Complete blood counts (CBC) were obtained at least every other day on inpatients. Outpatients had a CBC performed every week until recovery of blood counts or until onset of fever. The longer interval between blood counts in ambulatory patients did not allow a precise assessment of the true nadir or duration of neutropenia.

TMZ–E or P was instituted coincident with the start of cytotoxic therapy. The oral regimen was continued until any of the following end-points was reached: (1) recovery of absolute neutrophil count to $>500/mm^3$, (2) onset of fever (defined as a single oral temperature elevation above 38.5°C or three elevations above 38.0°C within a 24-hour period) or clinical signs of infection, or (3) development of any serious reaction suggestive of drug allergy. Patients who became febrile had cultures of the blood, urine, nose, throat, and rectum performed immediately, and weekly thereafter. Other sites were cultured depending on clinical indication. The prophylactic oral medications were then discontinued and parenteral broad spectrum antibiotics were instituted. On the basis of the initial evaluation and culture results, fever was categorized with regard to etiology as follows: (1) fever without documented source (FUO), (2) clinical infection without microbiologically isolated agent, (3) microbiologically documented infection without sepsis, and (4) sepsis (as defined by at least one positive blood culture).

Outpatients were asked to bring their medications on each clinic visit so that pill counts could be performed. Outpatients were also called at home by one of the investigators (A.J.) to inquire about and to encourage compliance. Inpatients were monitored daily by protocol staff. Compliance for each treatment episode was rated at the end of the study period as follows: excellent (E): every pill taken as prescribed; good (G): at least 75% of doses taken over the study period; poor: less than 75% of doses taken; or protocol discontinued: no pills taken for more than 24 hours prior to study end-point by decision of patient or of protocol staff (in the case of severe adverse reaction), regardless of previous compliance.

At the conclusion of the trial, the results were tabulated and statistically evaluated prior to breaking the randomization code. Comparison of medians was done by the Wilcoxon rank sum test and comparison of proportions by the chi-square method with Yates' correction for small samples. Two-sided significance levels were employed in computing P values for all tables; P values not displayed are >0.05.

Results

There were a total of 66 protocol entries, 31 on to P and 35 on to TMZ–E. Of the P group, two episodes were excluded from analysis: one patient decided immediately after randomization not to participate; one patient could take no oral medications due to chemotherapy-induced emesis and became febrile before oral medication could be started. Of the TMZ–E group, eight treatment episodes were excluded from analysis of antibiotic efficacy: three patients decided against participation immediately after randomization; infection was diagnosed in one patient after a single dose and in another prior to the first dose; one patient was lost to follow-up after randomization; one was already receiving isoniazid, rifampin, and ethambutol for pulmonary *Mycobacterium fortuitum;* one patient developed intense pruritis after the first dose and refused further participation. This last patient was included in analysis of adverse side effects (Table 2). Therefore, 29 placebo-treated episodes (23 patients) and 27 drug-treated episodes (22 patients) were available for analysis of prophylactic antibiotic efficacy.

Characteristics of the two study groups are indicated in Table 1. The TMZ–E group included relatively more episodes of treatment for acute leukemia (17/27 *vs* 8/29 for P, $P < 0.025$). Nevertheless, the number of leukemics in each group undergoing the most intense therapy for a grossly diseased marrow (induction or reinduction) was the same. Although the median number of total days spent at ≤ 500 neutrophils/mm^3 was somewhat longer in the TMZ–E group, being 13 *versus* 7 (mean 13.5 *versus* 10.1) for the P group, this was not statistically significant, nor was there any significant difference in the median number of total days spent at <100 neutrophils/mm^3 (TMZ–E 6.5 *vs* P 2; mean 9.1 *vs* 6.1), thus indicating that the intensity of chemotherapy in the two groups was comparable.

The oral prophylactic regimen was administered only until the first evidence of fever or infection, or until recovery of the neutrophil count to above $500/mm^3$. Thus, this "on-study" period is the only time that can be examined for a possible protective effect by TMZ–E. The median number of days on-study was 15 for TMZ–E *versus* 12 for P. During this period the incidence and duration of neutropenia was not significantly different between placebo-treated and drug-treated groups. Though the median nadir count was lower in the drug group than in the P group (Table 3), differences were not statistically significant. Patients with solid tumors attained an on-study nadir of <500 neutrophils/mm^3 in 70% of episodes in both groups (TMZ–E 7/10, P 15/21), whereas acute

TABLE 2. Adverse Reactions

All Episodes	Placebo	TMZ-E
Total no. of episodes	29	28*
Total no. of patients	23	23*
Episodes with adverse reaction (no. /total no. of episodes)	3/29	18/28†
Patients with adverse reaction (no./total no. of patients)	3/23	15/23‡
Incidence protocol discontinuation due to adverse reaction (no./total no. of episodes)		
By staff	0/29	5/28
By patient	1/29	2/28
Total	1/29	7/28§
Episodes with gastrointestinal reaction any type (no./total no. of episodes)	2/29	10/28‖
No. of episodes with		
Nausea and vomiting	1	7¶
Abdominal discomfort	1	4
Diarrhea	1	2
No. of episodes with skin reaction per total no. of episodes	1/29	7/28§

TMZ-E: oral trimethoprim-sulfamethopazole (Bactrim) plus erythromycin.

* All 27 treatment episodes (in 22 patients) plus 1 additional episode in a drug recipient who was excluded from analysis of drug efficacy because protocol was discontinued after a single dose, due to intense pruritus.

† $\chi^2 = 15.571$, $P < 0.0005$.

‡ $\chi^2 = 11.044$, $P < 0.001$.

§ $\chi^2 = 3.843$, $P = 0.05$.

‖ $\chi^2 = 5.490$, $P < 0.025$.

¶ $\chi^2 = 3.843$, $P = 0.05$ results not significant; these tests were not independent. To maintain an overall 0.05 significance level, an adjusted alpha level < 0.05 was required.

leukemic patients attained on-study nadirs of <500 neutrophils/mm^3 in 88% of episodes (TMZ-E 15/17, P 7/8).

Those episodes in which compliance was E or G were then considered separately, in order to assess efficacy of the prophylactic regimen when properly taken. This excluded a comparatively large fraction of drug recipients (12/27 TMZ-E *vs* 3/29 P; $P < 0.01$), five of whom complied poorly and seven in whom the protocol was halted due to intolerable side effects (Tables 1 and 2). The incidence, degree, and total duration of neutropenia were similar between drug and placebo recipients in the E + G category (Table 3).

Antibiotic Efficacy

Whether all episodes or only those with E + G compliance are considered, there was no significant difference in the incidence of fever between recipients of TMZ-E or of P, regardless of the level of neutropenia (Table 4). The incidence of fever was high, with 63% of all episodes (67% TMZ-E, 59% P) culminating in fever. In contrast, only 54% of all E + G episodes ended with fever, reflecting the fact that patients who could not comply well developed fever almost uniformly (10/12 TMZ-E, 3/3 P). Median days from onset of neutropenia to onset of fever was not significantly different between the regimens, regardless of compliance (3.5 days TMZ-E *vs* 4 days P, all episodes; 2 days TMZ-E *vs* 4.5 days P, E + G episodes). The proportion of clinically or microbiologically documented infections in febrile episodes was significantly lower in the TMZ-E group (4/18) *versus* the P group (11/17) at $P < 0.05$, for all episodes. This tendency was also present in the E + G episodes (2/8 TMZ-E *vs* 10/14 P) though not statistically significant by two-tailed chi-square analysis ($P = 0.08$). When all episodes with an on-study neutrophil nadir <500/mm^3 were compared according to histologic diagnosis, there was no significant difference in fever incidence in solid tumor patients (TMZ-E 5/7

TABLE 3. Episodes Compared According to Level and Duration of Neutropenia

	All episodes		E + G episodes	
	Placebo	TMZ-E	Placebo	TMZ-E
Nadir on-study*				
≤500 neutrophils/mm^3	22 (76%)	22 (82%)	19 (73%)	11 (73%)
≤100 neutrophils/mm^3	14 (48%)	15 (55%)	11 (42%)	5 (33%)
Absolute count†	222 (0–1840)	20 (0–3182)	232 (0–1840)	195 (0–1382)
Days on-study‡				
All days (range)	12 (2–53)	15 (6–39)	15.5 (2–53)	18 (6–39)
At ≤500 neutrophils/mm^3	4 (0–9)	4 (0–26)	4 (0–9)	2 (0–15)
At ≤100 neutrophils/mm^3	0 (0–7)	1 (0–12)	0 (0–7)	0 (0–11)
Total days§ at				
≤500 neutrophils/mm^3	7 (0–32)	13 (0–50)	6 (0–32)	9 (0–21)
≤100 neutrophils/mm^3	2 (0–27)	6.5 (0–48)	0.5 (0–27)	2 (0–19)

E: excellent; G: good; TMZ-E: oral trimethoprim-sulfamethoxazole (Bactrim) plus erythromycin.

* No. of episodes (percent of total episodes).

† Median number (range) segmented neutrophils and bands/mm^3, prior to study end-point.

‡ Median number (range) days.

§ Median number (range) days of total period of neutropenia, including those beyond study end-point in episodes culminating with fever.

TABLE 4. Outcome

	All episodes		E + G episodes	
	Placebo	TMZ-E	Placebo	TMZ-E
Fever incidence/total no. of episodes				
All episodes (percent)	17/29 (59%)	18/27 (67%)	14/26 (54%)	8/15 (53%)
Nadir on-study				
≤500 neutrophils/mm³	14/22	16/22	11/19	7/11
≤100 neutrophils/mm³	13/14	11/15	10/11	3/5
*Days to onset of fever				
All days (range)	10 (2–17)	12 (6–18)	9.5 (2–17)	10.5 (6–18)
At ≤500 neutrophils/mm³	4 (0–9)	3.5 (0–16)	4.5 (0–9)	2 (0–10)
At ≤100 neutrophils/mm³	2 (0–7)	1.5 (0–10)	1.5 (0–7)	0 (0–9)
Fever source/total no. of febrile episodes				
Fever without documented source	6/17	14/18†	4/14	6/8‡
Clinically infected	4	0	3	0
Microbiologically infected, no sepsis	4 11/17	3 4/18	4 10/14	1 2/8
Sepsis	3	1	3	1
Death from infection/total no. of episodes	1/29	3/27	1/26	2/15

TMZ-E: oral trimethioprim-sufamethoxazole (Bactrim) plus erythromycins.

* Median no. of (range) days prior to fever spike in episodes culminating with fever.

† $\chi^2 = 4.825$, $P < 0.05$.

‡ $\chi^2 = 2.752$, $P = 0.08$.

vs P 8/15, $P > 0.70$) or in patients with acute leukemia (TMZ-E 11/15 *vs* P 6/7, $P > 0.95$). Likewise, there was no significant difference in episodes of documented infection according to histologic diagnosis. Overall, 6/22 granulocytopenic episodes in solid tumor patients ended with documented infections *versus* 9/22 granulocytopenic episodes in leukemia patients (TMZ-E 1/7 *vs* P 5/15 in solid tumor patients, TMZ-E 5/15 *vs* P 4/7 in leukemia patients).

The number of deaths from infection in each group did not differ significantly. Infectious deaths occurred in 3/27 drug-treated episodes; two patients died with solid tumors and one with acute myelogenous leukemia in relapse. One infectious death occured in 29 placebo-treated episodes; a patient with oat cell lung cancer died of tuberculosis.

There were two additional deaths in autologous marrow transplant patients in the TMZ-E group; one patient received high-dose BCNU (1,3-bis-[2-chloroethyl]-1-nitrosourea) and another received high-dose mitomycin-C. Death was due to severe hepatic failure in each case, which was believed to be chemotherapy induced.[20]

Microbial Isolates

Regarding the sites of infection and microbial isolates (Table 5), the small numbers do not permit statistically significant comparisons, but certain trends are discernible. Gram-positive coccal infections, four in all, were caused by *S aureus*, except for one *Streptococcus viridans* in the placebo group, and all gram-positive cocci were sensitive to erythromycin in both groups. The two gram-negative infections in TMZ-E recipients were due to an *Escherichia coli* (TMZ-sensitive) perirectal abscess and a *P aeruginosa* bacteremia. In P recipients the three gram-negative infections were as follows: *P aeruginosa* bacteremia, *Klebsiella oxytoca* (TMZ-sensitive) cellulitis with bacteremia, and *Proteus vulgaris* (sensitivity not tested) urinary infection. A single case of disseminated candidiasis occurred, this in the TMZ-E group.

TABLE 5. Infections and Colonization

	Placebo	TMZ-E
Total episodes with documented infection	11	4
Sites infected (no.)		
Oropharynx	1	2
Sinus	1	0
Middle ear	1	0
Pulmonary	1	1
Small bowel	1	0
Anorectal	1	2
Urinary	1	0
Cellulitis	2	0
Skin incision	1	0
Central IV catheter	1	0
Blood	3	1
Pathogens (no.)		
Gram-negative rods	3	2
Gram-positive cocci	4	1
Bacteriodes fragilis	0	1
Mycobacterium t.b.	1	0
Candida species	0	1
Colonization with candida (no./total episodes)		
All episodes	2/29	6/27
All episodes (no oral Mycostatin)	2/24	6/19
E + G episodes	1/26	5/15*
E + G episodes (no oral Mycostatin)	1/22	5/13†

TMZ-E: oral trimethoprim-sulfamethoxazole (Bactrim) plus erythromycin; E: excellent; G: good.

* $\chi^2 = 4.4706$, $P < 0.05$.

† $\chi^2 = 4.4452$, $P < 0.05$.

Analysis of fungal colonization was complicated by the fact that some patients received oral mycostatin prophylaxis during the on-study period. Considering only episodes in which prophylactic oral mycostatin was not used, oral candidiasis occurred more frequently in the TMZ–E group (6/19) than in P-treated controls (2/24) The trend became statistically significant when E + G compliers were considered separately (5/13 TMZ–E *vs* 1/22 P, $P < 0.05$, as shown in Table 5.

Toxicity

Adverse reactions were documented in a significantly higher proportion of the drug-treated group, whether considered by episode (18/28 TMZ–E *vs* 3/29 P, $P < 0.0005$) or by patient (15/23 TMZ–E *vs* 3/23 P, $P < 0.001$), as shown in Table 2. Gastrointestinal complaints, particularly nausea and vomiting, were frequent. Nausea and vomiting were only considered to be toxic results of the prophylactic regimen if they occurred at least several days after the resolution of chemotherapy-induced symptoms, or if they specifically and immediately followed pill consumption during chemotherapy. A higher incidence of skin reactions was also noted in drug-treated episodes (7/28) than in placebo (1/29). Skin reactions among the seven TMZ–E episodes were diffuse maculopapular rash in five, urticaria in one, and intense pruritus without rash in one. Side effects were sufficiently severe to cause discontinuation of the protocol in 25% (7/28) of episodes in the drug-treated group.

Discussion

The efficacy, toxicity, and practicality of TMZ–E *versus* P were assessed in a strictly prophylactic setting. No infected or febrile patients were entered into the study, and the regimen was discontinued at the onset of fever. Under these circumstances, fever incidence was neither significantly different between TMZ–E and P recipients, regardless of degree of neutropenia, nor did TMZ–E delay the onset of fever. The unexpectedly poor compliance with the drug regimen made it necessary to test the hypothesis of TMZ–E efficacy, per se, when the regimen was taken properly. Data from the E + G compliance subset show that TMZ–E was ineffective. However, the cause of fever was less frequently documented in TMZ–E recipients than in controls, suggesting that the prophylactic regimen may impair the ability to document the infectious source. This pattern has been apparent in other series using TMZ.[11–14]

Despite the shift in the pattern of fever etiology from documented infection to fever of undetermined origin, death from infection was no less frequent in the TMZ–E group. In our experience, there appears to be no practical benefit to converting a potentially apparent infection into an FUO; the management of fever in this setting, where the host's immune response is often blunted, requires no less aggressive an approach than does obvious infection.[3,4,21–25] TMZ–E may simply obscure the cause of fever, perhaps by interference with *in vitro* cultures, and by masking physical signs of infection. The ability of oral antibiotic therapy to suppress initial blood culture positivity in patients with bacterial endocarditis has been recently documented.[26]

Of possible concern is the finding that a significant number of our TMZ–E recipients developed oral candidiasis. This result is in keeping with earlier studies in patients given long-term TMZ prophylaxis for *Pneumocystis*.[27] Moreover, in our study, the only case of disseminated candidiasis occurred in the TMZ–E group.

Variations in experimental design and patient population may explain some differences between our findings and those of other published trials of TMZ-based regimens. The current trial included a large proportion of solid tumor patients in addition to acute leukemic patients in various stages of treatment. Although Gurwith and coworkers[14] reported a protective effect of TMZ in neutropenic adult cancer patients, the advantage was not statistically significant in their patients with solid tumors. Though our solid tumor patients were treated with chemotherapy regimens more intense than conventional therapies, including some requiring autologous marrow reinfusion, the median number of neutropenic days for all patients in the TMZ–E and P groups was still less than in several of the series confined to patients with primary bone marrow disease.[11–13] In this regard, the results of the trial conducted by Weiser and associates,[15] in patients with acute leukemia in remission undergoing consolidation therapy, are pertinent. The mean duration of neutropenia was substantially shorter than in earlier trials, and the incidence of fever was the same in TMZ recipients as in controls. Nevertheless, the incidence of fever requiring the institution of broad spectrum antibiotics in our series (TMZ–E group 67%, P group 59%) is very similar to the incidence reported in other series comparing trimethoprim–sulfamethoxazole with controls receiving no prophylactic antibacterial therapy. The incidence of fever during granulocytopenic episodes for control patients was reported as 61%, about 60% and 41% by Dekker and associates,[13] Gurwith and associates[14] and Weiser and associates,[15] respectively. Thus the risk of fever during granulocytopenia is comparable between this and other series.

Few of the earlier studies have examined compliance carefully. Wade and associates[8] reported 94% compliance with oral TMZ–mycostatin compared with only 73% with oral gentamicin–mycostatin. However, we found compliance with our regimen to be a considerable problem, perhaps due to the inclusion of erythromycin. The most frequent side effects were nausea and vomiting, and skin reactions. Overall, the ability of the TMZ–E group to comply with even 75% of doses was poor, with only 56% (15/27) of TMZ–E episodes rating *E* or *G* compared with

90% (26/29) of P episodes. Regardless of the theoretical question of TMZ–E efficacy in preventing fever, the poor tolerance of this combination renders its usefulness doubtful. Of course, it is possible that some of the outpatients could discard their medication prior to a pill count. Perhaps compliance in the TMZ–E group was even worse than patients reported. Nevertheless, considering the close contact maintained by a single investigator with all outpatients, we feel that such potential bias was kept at an absolute minimum within the confines of an outpatient setting.

Other investigators do not report compliance with pill consumption but point to the marked reduction in enteric gram-negative flora as an index of "effective" compliance.[12,13,15,28] However, the recently concluded National Cancer Institute study[19] demonstrated that compliance was an independent predictor of outcome, suggesting that the inability to comply with an oral regimen is itself a risk factor. Additional controlled trials which correlate carefully determined compliance rates with alterations in enteric flora and with the incidence of fever and infection would be helpful.

The emergence of bacterial infections resistant to TMZ or E was not seen in our trial, but must still be considered a major potential complication in any prophylaxis scheme. A recently published study conducted in a healthy student population in Mexico[29] showed that 2 weeks of oral TMZ led to high-level drug resistance to multiple antibiotics in fecal *E coli* without reducing the total gram-negative flora. Neutropenic patients who are already infected on beginning TMZ prophylaxis may be prone to the development of plasmid-induced multiply-resistant bacterial infections.[30]

In conclusion, it seems likely that oral prophylaxis with TMZ–E in adult neutropenic cancer patients is ineffective. Moreover, this drug combination is associated with substantial toxicity, making compliance difficult. Finally, this drug combination may obscure the cause of infection in neutropenic patients who become febrile.

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