

- Amin HM, Medeiros LJ, Ma Y, et al. Inhibition of JAK3 induces apoptosis and decreases anaplastic lymphoma kinase activity in anaplastic large cell lymphoma. *Oncogene*. 2003;22:5399-5407.
- Amin HM, Lai R, Lin Q, Feretzaki M, Grammatikakis I, Medeiros LJ, Rassidakis GZ. JAK3 activation is significantly associated with ALK expression in anaplastic large cell lymphoma [abstract]. *Mod Pathol*. 2004;17:238A.
- Chim C-S, Fung T-K, Cheung W-C, Liang R, Kwong YL. SOCS1 and SHP1 hypermethylation in multiple myeloma: implications for epigenetic activation of the Jak/STAT pathway. *Blood*. 2004;103:4630-4635.
- Catlett-Falcone R, Landowski TH, Oshiro MM, et al. Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity*. 1999;10:105-115.
- Oka T, Ouchida M, Koyama M, et al. Gene silencing of the tyrosine phosphatase SHP1 gene by aberrant methylation in leukemias/lymphomas. *Cancer Res*. 2002;62:6390-6394.
- Koyama M, Oka T, Ouchida M, et al. Activated proliferation of B-cell lymphomas/leukemias with the SHP1 gene silencing by aberrant CpG methylation. *Lab Invest*. 2003;83:1849-1858.

## To the editor:

### Elimination of *Aspergillus* infection in allogeneic stem cell transplant recipients with long-term itraconazole prophylaxis: prevention is better than treatment

In their single-center report of antifungal prophylaxis after allogeneic stem cell transplantation (SCT),<sup>1</sup> Marr et al refer to our multicenter randomized trial.<sup>2</sup> However, the authors failed to note important differences between our study and theirs. In our study,<sup>2</sup> we used a dose of oral itraconazole solution (200 mg 2 times daily) that was lower than the dose used by the Seattle group and administered it only after transplantation. Patients unable to tolerate oral medications were switched back to the intravenous form of itraconazole or fluconazole and not removed from the study. Despite a lower dose of itraconazole, mean trough plasma concentrations of itraconazole were greater than the 500-ng/mL level targeted for prophylactic efficacy.<sup>3</sup> Proven invasive fungal infections occurred in 9% of the itraconazole patients and 25% of the fluconazole patients during the first 180 days after transplantation. The incidence of *Aspergillus* infection was reduced from 12% in the fluconazole group to 4% in the itraconazole group. Except for more frequent gastrointestinal side effects, itraconazole was well tolerated. The incidences of drug-related hepatotoxicity and renal toxicity were low in our study and much less than those reported by Marr et al. The incidences of hepatotoxicity in both the fluconazole patients and the itraconazole patients reported by the Seattle group were extremely high and much greater than those reported by this group and others in previous studies.<sup>3-6</sup> Thus, other factors besides fluconazole or itraconazole were likely responsible for liver dysfunction in most of their patients.

On the basis of our results, we introduced long-term itraconazole as routine antifungal prophylaxis in all adult patients undergoing an allogeneic SCT at the University of California, Los Angeles (UCLA). Intravenous itraconazole (200 mg intravenously every 12 hours for 2 days followed by 200 mg intravenously every 24 hours) is started on day 1 after SCT and continued until time of engraftment. After engraftment, patients receive oral itraconazole solution (200 mg every 12 hours) until day 100 after transplantation. After day 100, oral itraconazole is continued in patients still requiring corticosteroids for prevention or treatment of graft-versus-host disease (GVHD). Both inpatients and outpatients unable to take oral therapy are returned to intravenous itraconazole. From December 2001 to December 2003, 73 allogeneic SCT patients received itraconazole prophylaxis. These patients were at high risk for *Aspergillus* infection (median age, 40 years; range, 18-64 years; advanced disease, 78%; previous SCT, 20%; unrelated donor,

41%; high-dose corticosteroids for prevention or treatment of GVHD, 86%; grades II-IV GVHD, 45%). None of the patients developed *Aspergillus* infection, which is significantly lower than the incidence of *Aspergillus* infection in similar UCLA allogeneic SCT patients receiving fluconazole prophylaxis before December 2001 (0% vs 13%;  $P = .004$ ). The only invasive fungal infections were 3 cases of candidemia (2 itraconazole sensitive, 1 itraconazole resistant). Overall survival was 55%, but no deaths were related to fungal infection. Except for nausea and vomiting (19% incidence), itraconazole was well tolerated. There were no cases of hepatotoxicity or renal toxicity attributable to itraconazole, and we did not find it necessary to routinely monitor serum drug levels.

In summary, we conclude that *Aspergillus* can be safely eliminated as a significant pathogen in allogeneic SCT recipients when prophylactic itraconazole is administered at a tolerable dose and started after the day of transplantation. In view of the difficulty of treating established *Aspergillus* infections in highly immunosuppressed patients, we believe that prevention of infection is clearly better than treatment.

Drew J. Winston, Christos Emmanouilides, Kathy Bartoni,  
Gary J. Schiller, Ronald Paquette, and Mary C. Territo

Correspondence: Stem Cell Transplant Program, Division of Hematology-Oncology, Department of Medicine, UCLA Medical Center, Los Angeles, CA 90095; e-mail: dwinston@mednet.ucla.edu.

## References

- Marr KA, Crippa F, Leisenrings W, et al. Itraconazole versus fluconazole for prevention of fungal infection in patients receiving allogeneic stem cell transplants. *Blood*. 2004;103:1527-1533.
- Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients: a multicenter randomized trial. *Ann Intern Med*. 2003;138:705-713.
- Glasmachner A, Prentice A, Gorschluter M, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. *J Clin Oncol*. 2003;21:4615-4626.
- Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med*. 1992;326:845-851.
- Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infection after marrow transplantation—a prospective, randomized, double-blind study. *J Infect Dis*. 1995;171:1545-1552.
- Winston DJ, Busuttill RW. Randomized controlled trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients. *Transplantation*. 2002;74:688-695.

## Response:

### Prevention of aspergillosis

We agree with Winston et al's emphasis on prevention; however, we do not agree that the data available definitively demonstrate the superiority of itraconazole. The design of our trial impacted the overall outcomes. Most important was the use of antifungals during conditioning, given the trend to early toxicities in itraconazole recipients who received cyclophosphamide.<sup>1,2</sup> This trend appeared to decrease in patients enrolled after the protocol was modified to initiate antifungals after conditioning; however, there were too few patients enrolled to enable comparisons.

We do not have the data necessary to compare toxicities between the 2 trials. Winston et al<sup>3</sup> reported the adverse events thought possibly to be related to the study drugs, and we reported the number of patients who developed toxicities independent of cause. More itraconazole recipients developed tripling of baseline total bilirubin (143 of 151, 95%) compared with fluconazole recipients (128 of 143, 86%;  $P = .02$ ). The incidence of hepatotoxicities in patients who received fluconazole is not different compared with similar patients in our center<sup>4</sup>; the high proportion reflects the definition of "hepatotoxicity."

Despite the differences in timing and dosing of antifungals in the 2 trials, the outcomes of patients who received itraconazole were remarkably similar. Both studies reported high rates (24%) of gastrointestinal (GI) side effects. Also, the invasive fungal infection (IFI) incidences in itraconazole recipients were not different (13% vs 9%). The only large difference was the incidence of IFI in fluconazole recipients (16% vs 25%, Winston et al study<sup>3</sup>). Outcomes in the Winston et al study were driven by an unusually high number of candidemias (8 of 67 patients, 12%)—much greater than in our study (2.6%) or in prior trials.<sup>5,6</sup>

While we have learned important lessons, we do not think that the data generated by either trial support the conclusion that itraconazole prophylaxis is a better strategy. In the Winston et al study,<sup>3</sup> outcomes may have been impacted by bias between the patients randomized, as more fluconazole recipients received unrelated donor transplants (likewise, increased graft-versus-host disease [GVHD] and therapies). Moreover, the 140 patients enrolled did not provide the power to demonstrate superiority. Finally, it is notable that the apparent IFI protection was not associated with a trend to improved survival. We believe that the conclusion of superiority should be supported at least by a trend toward decreased transplant-related mortality in order to negate the

possibility that decreased infection rates are associated with excessive antifungal-related toxicities.

The data presented for the 73 follow-up patients are compelling. Based on the results of Winston et al's trial, we would expect at least 4 IFIs in this cohort. This raises questions: What were the methods of surveillance and the duration of follow-up? Were there other patient or environmental factors that changed? Without having a contemporaneous control, it may be difficult to identify the causative factor(s).

We agree with the assertion that prevention is better than treatment, and we are intrigued by the trends in the Winston et al study<sup>3</sup> and the subset of patients enrolled later in our trial. However, we believe that policy decisions should be based on data obtained from properly designed randomized trials rather than trends demonstrated in underpowered studies or retrospective cohort analyses. It is not clear to us that the risk-benefit ratio favors itraconazole for prophylaxis, but we share our colleagues' enthusiasm that a newer azole may accomplish our common goal of preventing aspergillosis.

**Kieren A. Marr and Michael Boeckh**

*Correspondence: Kieren Marr, Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, D3-100, Seattle, WA 98109.*

### References

- Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is affected by azole antifungals. *Blood*. 2004;103:1557-1559.
- Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood*. 2004;103:1527-1533.
- Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients: a multicenter, randomized trial. *Ann Intern Med*. 2003;138:705-713.
- McDonald G, Schoch H, Gooley T. Liver dysfunction and mortality after allogeneic marrow transplantation: analysis of 1419 consecutive patients [abstract]. *Hepatology*. 1999;30:162A.
- Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. *J Infect Dis*. 1995;171:1545-1552.
- Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med*. 1992;326:845-851.

## To the editor:

### Phosphatidylserine externalization in cardiophilin-deficient cells

We were intrigued by the recent article by Kuijpers et al<sup>1</sup> on the binding of annexin V to neutrophils obtained from Barth syndrome patients. The authors reported that freshly isolated neutrophils from these patients were readily labeled with annexin V (a phosphatidylserine [PS]-binding protein) in the absence of other indices of apoptosis and concluded that these cells expose an alternative ligand for annexin V that is distinct from PS. We suggest that other, recent findings could be invoked to explain these novel observations in cardiophilin (CL)-deficient Barth syndrome cells.

PS externalization is an important "eat me" signal on apoptotic cells and serves to alert neighboring macrophages. Neutropenia (reported to be a common finding in Barth syndrome, albeit not a prominent feature in the cohort examined by Kuijpers et al) could thus be linked to the aberrant exposure of PS on circulating neutrophils. Conversely, the lack of PS externalization in neutrophils from chronic granulomatous disease (CGD) patients could contribute to defective clearance and the formation of granulomas in these individuals.<sup>2</sup> However, Kuijpers et al argue that annexin V