lar the survival of mature hematopoietic cells, was unexpected and intriguing. Limited numbers of cells were available at very late time points to perform molecular and cellular analyses and the mechanism of action for this pro-survival role of hTERT is as yet unknown. A pro-survival action of hTERT independent of telomerase enzymatic activity has recently been described in human breast cancer cells.7 Future studies aim to elucidate the cellular and molecular mechanisms underlying this pro-survival effect of hTERT in human hematopoietic progenitor cells.

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Infectious Disorders

Clinical significance of breakthrough fungemia caused by azole-resistant Candida tropicalis in patients with hematologic malignancies

A 5-year retrospective analysis of fungemia in patients with hematologic malignancies revealed that four patients, who received fluconazole and itraconazole during neutropenia, developed breakthrough candidemia due to azole-resistant Candida tropicalis isolates. This observation suggests that causative organisms of candidemia in neutropenic patients receiving azoles should be suspected of being azole-resistant.

References

before the diagnosis of candidemia, suggesting colonization of the strains in the digestive tract. All patients developed mucositis due to chemotherapy. The patients received oral itraconazole (150–200 mg/day) as antifungal prophylaxis and therapy for 35–105 days. At the time of becoming febrile, the patients were given pre-emptive intravenous fluconazole (400 mg/day) for 5–16 days. Intravenous amphotericin B was administered at the dosage of 50 mg/day for 33–101 days after fluconazole was discontinued because of persistent high fever. Two patients developed breakthrough candidemia despite receiving fluconazole and itraconazole and the other two patients developed breakthrough candidemia despite receiving itraconazole and amphotericin B. Overall, two patients responded to amphotericin B with neutrophil recovery.

It is interesting to note that all patients received both itraconazole and fluconazole before developing fungemia caused by azole-resistant \( C.\) tropicalis. Some studies have shown that fungemia in cancer patients caused by fluconazole-resistant Candida species is associated with exposure to fluconazole administered for prophylaxis or therapy.\(^2,7\) Even \( C.\) albicans, which is generally susceptible to azole compounds, has been reported to cause breakthrough fungemia due to fluconazole-resistant strains in immuno-

### Table 1. Clinical and in vitro susceptibility data of the four isolates from four patients with fungemia caused by azole-resistant \( C.\) tropicalis.

<table>
<thead>
<tr>
<th>Patient age/gender (Year)</th>
<th>Hematologic malignancy</th>
<th>Possible risk factors for fungemia</th>
<th>Surveillance culture</th>
<th>MICs (µg/mL)</th>
<th>Antifungal prophylaxis and therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flu Itr Vor Amp Micf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: 76/M (1996)</td>
<td>AML</td>
<td>Chemotherapy, antibiotic use, CVC, steroid use, mucositis, neutropenia for 86 days</td>
<td>≥64 ≥32 ≥32 ≥32</td>
<td>0.03125 0.0625</td>
<td>Itr, 150 mg q.d. for 91 days</td>
<td>Survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flu, 400 mg q.d. for 16 days</td>
<td>Amp, 50 mg q.d. for 75 days</td>
<td></td>
</tr>
<tr>
<td>2: 40/M (1997)</td>
<td>AML</td>
<td>Chemotherapy, antibiotic use, CVC, steroid use, mucositis, neutropenia for 29 days</td>
<td>≥64 ≥32 ≥32 ≥32</td>
<td>0.0625 0.0625</td>
<td>Itr, 150 mg q.d. for 35 days</td>
<td>Unrelated death 3 months after diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flu, 400 mg q.d. for 5 days</td>
<td>Amp, 50 mg q.d. for 33 days</td>
<td></td>
</tr>
<tr>
<td>3: 63/F (1997)</td>
<td>AML</td>
<td>Chemotherapy, antibiotic use, CVC, mucositis, neutropenia for 97 days</td>
<td>≥64 ≥32 ≥32 ≥32</td>
<td>0.03125 0.0625</td>
<td>Itr, 200 mg q.d. for 105 days</td>
<td>Related death on day 2 after diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flu, 400 mg q.d. for 11 days</td>
<td>Amp, 50 mg q.d. for 101 days</td>
<td></td>
</tr>
<tr>
<td>4: 76/M (1998)</td>
<td>MDS</td>
<td>Chemotherapy, antibiotic use, CVC, steroid use, mucositis, neutropenia for 56 days</td>
<td>≥64 ≥32 ≥32 ≥32</td>
<td>0.03125 0.0625</td>
<td>Itr, 200 mg q.d. for 63 days</td>
<td>Related death on day 5 after diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flu, 400 mg q.d. for 11 days</td>
<td>Amp, 50 mg q.d. for 61 days</td>
<td></td>
</tr>
</tbody>
</table>

M: male; F: female; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; CVC: central venous catheter; Flu: fluconazole; Itr: itraconazole; Vor: voriconazole; Amp: amphotericin B; Micf: micafungin.
compromised patients receiving a short-term or long-term fluconazole. In addition, a recent in vitro study revealed that the acquisition of azole-resistance by *C. tropicalis* strains was rapid after culture in medium containing a high concentration of fluconazole. Therefore, in our cases, it is likely that the use of both fluconazole and itraconazole was effective against azole-susceptible *C. tropicalis*, but, it allowed potentially azole-resistant *C. tropicalis* to cause fungemia during neutropenia. Since colonization of *C. tropicalis* and mucositis were observed in all our patients before they developed fungemia, endogenous azole-resistant *C. tropicalis* could have been acquired through the digestive tract rather than from exogenous sources. Furthermore, RAPD typing demonstrated that each fungemia case was caused by a different strain of *C. tropicalis*, supporting an endogenous origin for the infections and negating the possibility of nosocomial transmission of a single strain.

As recently reported by Pfaller et al., many strains of fluconazole-resistant *C. albicans* display cross-resistance to itraconazole (RR-phenotype) and these RR-strains of *C. albicans* have proven to be less susceptible to new azoles such as voriconazole. It is surprising that our strains of *C. tropicalis* showed a RR-phenotype with high MIC of voriconazole. To our knowledge, voriconazole-insusceptible *C. tropicalis* has not been previously reported as a cause of breakthrough fungemia. These findings strongly imply that therapeutic options for fungemia caused by azole-resistant *C. tropicalis* are very limited, and, as shown in our study, amphotericin B and micafungin may be the most effective antifungal options.

In summary, immunocompromised patients who suffer breakthrough candidemia during the administration of azole antifungal agents should be suspected of harboring an azole-resistant strain until *in vitro* susceptibilities to the antifungal agents are determined.

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Key words: fungemia, Candida tropicalis, azole-resistance, hematologic malignancies.

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