Itraconazole Oral Solution Enhanced Vincristine Neurotoxicity in Five Patients with Malignant Lymphoma

Naoto Takahashi¹, Yoshihiro Kameoka¹, Yasuo Yamanaka¹, Kumi Ubukawa¹, Kunie Saito¹, Masumi Fujishima¹, Naohito Fujishima¹, Hirofumi Saito¹, Makoto Hirokawa¹, Stuart A. Scott² and Kenichi Sawada¹

Abstract

To prevent fungal infections in patients undergoing treatment for hematological malignancies, we investigated the use of oral itraconazole solution as opposed to itraconazole or fluconazole capsules. Herein, we report five lymphoma patients with severe vincristine neurotoxicity in strong association with oral itraconazole solution. Four patients suffered from severe myalgia with or without arthralgia which clinically resembled polymyalgia rheumatica. Two patients suffered from constipation due to subileus and one patient had a severe paralytic ileus. Appropriate management of the above symptoms, which included discontinuation of oral itraconazole solution, resulted in rapid recovery from neurotoxicity. Given the more consistent plasma concentrations of oral itraconazole solution when compared to itraconazole capsules and the ability of itraconazole to interfere with hepatic vincristine metabolism, we strongly recommend avoiding the combined administration of oral itraconazole solution and vincristine.

Key words: itraconazol oral solution, vincristine, neurotoxicity, polymyalgia rheumatica

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Introduction

Invasive fungal infections are a major cause of morbidity and mortality in patients with hematological malignancies receiving myelotoxic chemotherapy. The antifungal agent itraconazole has a broad spectrum of activity, which includes activity against Candida and Aspergillus, and is therefore an attractive antifungal prophylaxis for patients undergoing induction treatment for hematological malignancies. Despite the limited data on the efficacy of itraconazole-based systemic antifungal prophylaxis, it has been suggested that oral azole agents (e.g., fluconazole and itraconazole) are effective when treating patients with lymphoid malignancies and those who have undergone stem-cell transplantation (1, 2). Recently, an oral solution of itraconazole with improved absorption and bioavailability has been developed which produces more consistent plasma concentrations than the conventional itraconazole capsules (3).

The availability of oral itraconazole solution in April 2007 prompted our investigation of oral solution compliance compared with itraconazole capsules. Informed consent was obtained from each patient and the protocol was approved by the institutional review board of Akita University Hospital. Patients were given either oral itraconazole solution or itraconazole capsules intermittently for one-week periods and subsequently questioned about oral solution compliance by questionnaire. Within the total study cohort (n = 55), seven malignant lymphoma (ML) patients undergoing CHOP therapy were administered oral itraconazole solution. We identified enhanced vincristine neurotoxicity in five of these seven patients following co-administration with oral itra-
**Table 1. Summary of Clinical Events following CHOP and Itraconazole Treatment**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Duration of IT CZ administration(^a)</th>
<th>Duration of adverse effects (^b)</th>
<th>Ileus (^b)</th>
<th>Myalgia (^b)</th>
<th>Arthralgia (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65F</td>
<td>ALCL</td>
<td>from -8 to 5 of 5th CHOP</td>
<td>2 to 18</td>
<td>Grade2</td>
<td>Grade3</td>
<td>Grade3</td>
</tr>
<tr>
<td>2a</td>
<td>50F</td>
<td>DBLCL</td>
<td>since -15 of 3rd R-CHOP</td>
<td>4 to 15</td>
<td>Grade2</td>
<td>Grade3</td>
<td>Grade3</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td></td>
<td>since -36 of 4th R-CHOP</td>
<td>5 to 14</td>
<td>Grade2</td>
<td>Grade3</td>
<td>Grade3</td>
</tr>
<tr>
<td>3</td>
<td>46F</td>
<td>FL</td>
<td>from -8 to 7 of 1st CHOP</td>
<td>4 to 14</td>
<td>(-)</td>
<td>Grade3</td>
<td>(-)</td>
</tr>
<tr>
<td>4</td>
<td>51M</td>
<td>DLBCL</td>
<td>from -2 to 8 of 2nd R-CHOP</td>
<td>5 to 12+</td>
<td>(-)</td>
<td>Grade3</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>68F</td>
<td>DLBCL</td>
<td>from -2 to 5 of 1st R-CHOP</td>
<td>2 to 13</td>
<td>Grade3</td>
<td>(-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

*Time scale is in days from onset of CHOP therapy. \(^b\) Adverse effects are according to Common Terminology Criteria for Adverse Event v3.0.


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**Case Report**

The seven ML patients in our study cohort presented to the Akita University Hospital Hematology unit and received CHOP therapy (vincristine, doxorubicin, cyclophosphamide and prednisolone, with or without rituximab) at three-week intervals. In conjunction with CHOP, oral itraconazole solution (Janssen Pharmaceutical K.K.) was administered at a daily dose of 200 mg/person. Table 1 summarizes the time period of itraconazole administration and the six neurotoxic episodes which were observed in five of the seven patients. Four patients (cases 1, 2, 3 and 4) suffered from severe myalgia with or without arthralgia which clinically resembled polymyalgia rheumatica. However, given that prednisolone was ineffective at treating the polymyalgia rheumatica-like symptoms, Parotid pain was an early symptom of neurotoxicity in case 3. Two patients (cases 1 and 2) suffered from constipation due to subileus and one patient (case 5) had a severe paralytic ileus. Mild hyponatremia, Na 131 and 132 mEq/L, was observed in cases 4 and 5, respectively, and two patients (cases 2 and 5) developed hypertension secondary to myalgia and/or ileus. All had normal bilirubin, alkaline phosphatase, aminotransferases, creatine phosphokinase, C-reactive protein, and erythrocyte sedimentation rate. Coagulation problems and renal function were normal in all patients and there was no evidence of parvovirus B19 infection by serum analysis. Two patients (cases 2 and 5) temporarily required morphine treatment for pain and all five patients had an absence of deep reflexes following the onset of neurotoxic events. Appropriate management of the above symptoms, which included discontinuation of oral itraconazole solution, resulted in rapid recovery from neurotoxicity (day 15+/-3 of CHOP therapy); however, deep reflexes did not return for a minimum of four weeks. In all patients, the other courses of CHOP therapy were entirely performed without neurotoxicity after cessation of oral itraconazole solution.

As per the compliance protocol, patients receiving itraconazole capsules were administered the same dose as those receiving oral solution. Importantly, no neurotoxicity was observed in any of the patients undergoing CHOP therapy who received itraconazole capsules. The compliance protocol was discontinued in June 2007 following the occurrence of oral itraconazole solution-associated adverse effects.

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**Discussion**

To our knowledge, this is the first report of oral itraconazole solution-enhanced vincristine neurotoxicity in Japanese adults with hematological malignancies. The adverse drug reactions that we report are similar to those occasionally observed with vincristine-based therapy. However, it is important to note that although our patients were undergoing vincristine treatment, the severe neurotoxicity observed in the majority of our ML cohort did not emerge until the initiation of oral itraconazole solution prophylaxis.

Böhme et al first described enhanced vincristine neurotoxicity associated with itraconazole treatment in 1995 (4). In their report, severe neurotoxicity was observed in four out of 14 adult acute lymphocytic leukemia (ALL) patients who received induction chemotherapy (which included weekly vincristine injections) and antifungal prophylaxis with itraconazole capsules. It should be noted, however, that the capsule dose used in their report (400 mg/day) was twice the typical standard adult itraconazole dose (200 mg/day). Moreover, similar episodes of severe vincristine neurotoxicity have been reported in pediatric patients undergoing vincristine chemotherapy in combination with itraconazole prophylaxis (5-9). Recently, Chen et al reported itraconazole-enhanced vincristine neurotoxicity in two adult ALL patients (10). One patient received oral itraconazole solution and the other received itraconazole injection; however, the doses of itraconazole were not reported in their study (10). Our data strengthens these previous reports and indicates that oral itraconazole solution may, in part, be responsible for enhanced vincristine neurotoxicity.

The median plasma concentrations of itraconazole were
not measured in the present cases. However, the vincristine neurotoxicity observed in our patients was likely mediated by increased plasma concentrations of oral itraconazole solution when compared to itraconazole capsules (3). Moreover, oral itraconazole solution is absorbed more efficiently than itraconazole capsules. Taken together, the differences in bioavailability between the two compounds could explain why oral itraconazole solution was neurotoxic in our adult patients co-treated with vincristine.

Vincristine is metabolized by the hepatic cytochrome-P450 (CYP) 3A subfamily andazole antifungal prophylactics are potent inhibitors of fungal CYP3A isoenzymes (3, 11). Thus, it has been suggested thatazole antifungal agents, such as itraconazole, interfere with normal vincristine metabolism by inhibiting the human CYP3A4 and/or CYP3A5 enzymes, thereby enhancing vincristine neurotoxicity (11, 12). Another azole antifungal agent, fluconazole, also inhibits CYP3A-mediated metabolism of vincristine (13). However, the degree of inhibition is much less than that of itraconazole (13), consistent with the paucity of reports describing fluconazole-enhanced vincristine neurotoxicity.

In addition, the human CYP3A4 and CYP3A5 genes are highly polymorphic (14) and it is possible that certain variants CYP3A4 and/or CYP3A5 alleles are more susceptible to itraconazole-mediated inhibition than others. Heritable alleles with unique activities could facilitate interindividual differences in response to vincristine and itraconazole co-treatment. In our investigation of oral itraconazole solution, two of seven patients did not show any adverse side effects associated with vincristine co-treatment. We predict that interindividual differences in CYP3A activity as a result of germline CYP3A polymorphisms are responsible for this finding, however further study is necessary to test this hypothesis.

In conclusion, we report five lymphoma patients with severe vincristine neurotoxicity in strong association with oral itraconazole solution. Routine fluconazole and itraconazole antifungal prophylaxis has been reported in allogeneic transplant recipients (1, 2), yet there is no consensus regarding patients treated with standard CHOP and antifungal prophylaxis. Given the more consistent plasma concentrations of oral itraconazole solution when compared to itraconazole capsules and the ability of itraconazole to interfere with hepatic vincristine metabolism, we strongly recommend avoiding the combined administration of oral itraconazole solution and vincristine.

References


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