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Clinical Analysis of Adverse Drug Reactions between Vincristine and Triazoles in Children with Acute Lymphoblastic Leukemia

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Background: Vincristine (VCR) is a major chemotherapy drug for treatment of childhood acute lymphoblastic leukemia (ALL). Triazole antifungal drugs (AFD) are the main agents for the prevention/treatment of invasive fungal infection (IFI), a common complication during the treatment of ALL. This study investigated the adverse drug reactions (ADRs) between VCR and AFD.

Material/Methods: A retrospective study was performed on 68 children with ALL (39 boys and 29 girls, median age: 5 years) who were treated with VCR chemotherapy (a total of 136 cases, including both induction and reinduction phases) from January 2012 to December 2013 in our hospital. These cases were divided into 4 groups: the control group without AFD prevention/treatment (n=44), the Itra group receiving itraconazole oral solution (n=44), the Fluc group receiving intravenous fluconazole (n=42), and the Vori group receiving voriconazole oral tablets (n=6). The ADRs in each group was recorded and compared.

Results: The incidence of ADRs in the Itra and Vori groups were significantly higher compared with the Fluc and the control group (P<0.05). The incidence of ADRs in the Itra group was significantly higher than that in the Vori group, whereas there was no difference in the incidence between the Fluc and control group.

Conclusions: Given the lower incidence of ADRs between VCR and fluconazole compared with voriconazole or itraconazole, it is relatively safer to use fluconazole in ALL patients receiving VCR chemotherapy. The occurrence of ADRs should be closely monitored when triazoles must be administered concomitantly with VCR.

MeSH Keywords: Drug-Related Side Effects and Adverse Reactions • Triazoles • Vincristine

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2264 3 — 27

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Background

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and poses a serious threat to the health of children. With the development of multi-drug combination therapy in the past 50 years, the efficacy in children with ALL has been significantly improved and the current cure rate is close to 80%. Vincristine (VCR) is one of the most commonly used chemotherapy drugs in the induction and consolidation phases during the treatment of ALL. VCR is an alkaloid extracted from the periwinkle plant of the Apocynaceae family, which has been gradually applied in the treatment of various tumors since 1963. VCR is a cell cycle-specific anticancer drug that stops microtubule formation during mitosis by inhibiting polymerization of tubulin, and thereby suppresses the proliferation of tumor cells. VCR is predominantly metabolized in the liver by the cytochrome P450 (CYP) superfamily of enzymes and eliminated by the efflux transporter, P-glycoprotein (P-gp) [1,2].

With the increasing dose-intensity of leukemia chemotherapy and broad-spectrum antibiotic therapy, invasive fungal infections (IFIs) have become highly prevalent in patients with ALL. IFI is the most common complication and cause of death in children with malignant tumors during chemotherapy. Triazole agents such as fluconazole, itraconazole, and voriconazole are the most common antifungal drugs (AFDs), and are effective for the prophylactic and therapeutic therapy for IFIs. However, adverse drug interactions (ADRs) with the combination of VCR and triazole AFDs have been previously reported, including gastrointestinal toxicity, peripheral neuropathy, electrolyte abnormalities, cranial neuropathy, and seizures [3–9]. These severe toxicities are presumed to be related to the inhibitory effects of triazole AFDs on the metabolism of VCR through the cytochrome P450 (CYP) superfamily of proteins and their transport by P-glycoprotein (P-gp). Despite numerous reports on the deleterious drug combination, little is known about the clinical manifestation, prophylaxis, and management of its ADRs, especially in Chinese patients. Furthermore, few reports with large sample sizes have compared the incidence of various toxicities caused by this drug combination [10]. In this study, we performed a retrospective analysis on a large number of cases (136 cases) in our hospital in the past 2 years, and provided a comprehensive summary of toxicities, clinical manifestation, outcome, and management of the ADRs between VCR and triazole AFDs.

Material and Methods

Subjects

A retrospective study was performed on 68 children (39 boys and 29 girls) who were diagnosed with ALL and treated with VCR chemotherapy from January 2012 to December 2013 in our hospital. The median age was around 5 years (1.5–14 years). Each patient was treated with both induction and reinduction chemotherapy using VDLD regimen (VCR, daunorubicin or doxorubicin, L-asparaginase, and prednisone or dexamethasone) resulting in a total of 136 cases of treatments. These cases were divided into the following 4 groups: the control group without AFD prophylaxis/treatment (44 cases), the Itra group receiving itraconazole oral solution (44 cases), the Fluc group receiving intravenous fluconazole (42 cases), and the Vori group receiving voriconazole oral tablets (6 cases).

Concomitant administration of AFD with VCR

In 62 cases of induction chemotherapy, 1.5 mg/m^2 VCR (a maximum dose of 2 mg) was administered intravenously to patients at day 1, 8, 15, 22, and 29 using VDLD regimen. Itraconazole oral solution was administered in 32 cases (2.5 mg/kg, q12h) and intravenous fluconazole in 30 cases (8 mg/kg.d, qd) starting from day 1 of VDLD therapy. In 30 cases of reinduction chemotherapy, 1.5 mg/m^2 VCR (a maximum dose of 2 mg) was administered intravenously to patients at day 1, 8, 15, 22, and 29 using VDLD regimen. Itraconazole oral solution was administered in 12 cases (2.5 mg/kg, q12h), intravenous fluconazole in 12 cases (8 mg/kg.d, qd), and voriconazole oral tablets in 6 cases (4 mg/kg, q12h) starting from day 1 of VDLD therapy. Patients in the Vori group had already been taking voriconazole oral tablets prior to reinduction phase due to the occurrence of IFIs during the consolidation phase of chemotherapy. The occurrence of ADRs was strictly monitored and the time from first dose of VCR to clinical manifestations of ADRs was recorded in each case. The medication of triazoles in a patient was immediately terminated after the ADRs were observed. Full or partial recovery from the ADRs was recorded in each case.

Statistical analysis

Statistical analysis was performed using SPSS18.0 software. Differences in the age distribution and in the time elapsed from first dose of VCR to onset of ADRs among all groups were analyzed by t-tests. Differences in the age distribution and in the incidence of ADRs among groups were compared by chi-square tests. P values smaller than 0.05 were considered to be statistically significant.

Results

Summary of subjects

A total of 136 cases of interactions with VCR were recorded for the following triazole AFDs: Itraconazole (n=44), fluconazole (n=42), and voriconazole (n=6). The median age for

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Table 1. The age and sex distribution of patients.

	Different AFD groups			Control group	Total
	Itra group	Fluc group	Vori group		
Total number of cases	44	42	6	44	136
Median age * (range)	63 m (21 m–14 y)	59 m (19 m–10 y)	61 m (17 m–11 y)	63 m (16 m–13 y)	62 m (16 m–14 y)
1–3 years	14	14	2	14	42 (30.1%)
4–7 years	21	24	4	23	68 (50.0%)
7–14 years	9	4	0	7	26 (19.1%)
Male/female**	26/18	26/16	4/2	26/18	78/58

* Indicates P>0.05 in t-tests; ** indicates P>0.05 in chi-square tests using SPSS18.0 software.

Table 2. Summary of chemotherapy phase and the purpose for concomitant administration of AFD with VCR in ALL patients.

	Different AFD groups			Total
	Itra group	Fluc group	Vori group	
Total number of cases	44	42	6	92
Induction/reinduction	32/12	30/12	0/6	62/30
Prevention/treatment of IFIs	44/0	42/0	2/4	86/6

all patients was 5.2 years, with 30.9% of patients ≤3 years, 50% of patients 4–7 years, and 19.1% of patients 7–14 years. The age and sex distribution of the patients in all groups is summarized in Table 1, and no significant differences in the age and sex distribution were identified among these groups (P>0.05). The chemotherapy phase and purpose for concomitant administration of AFD with VCR in ALL patients are summarized in Table 2.

ADRs between AFDs and VCR

The median time elapsed from the first dose of VCR to clinical manifestations of ADRs between AFD and VCR was 8.5 days (range, 6–14 days) with itraconazole, 18.9 days (range, 15–22 days) with fluconazole, 9.2 days (range, 5–16 days) with voriconazole, and 20.8 days (range, 17–23 days) in the control group, suggesting that ADRs in the Fluc group occurred significantly later than those in the other 2 experimental groups (P<0.05). The median number of VCR doses administered before the onset of ADRs was 2 doses (range, 1–3 doses) for itraconazole, 3 dose (range, 2–4 doses) for fluconazole, and 2 doses (range, 1–3 doses) for voriconazole. The major types of ADRs in patients receiving VCR with triazole AFDs are summarized in Table 3, including gastrointestinal toxicity (48.91%), peripheral neuropathy (31.52%), electrolyte abnormalities (25%), autonomic neuropathy (22.83%), cranial neuropathy (14.13%), and seizure (8.7%). The most common manifestation of gastrointestinal symptoms was constipation, abdominal pain, ileus, hepatitis, and vomiting, whereas typical symptoms of peripheral neuropathy included arthralgia, back pain, limb weakness, and muscle spasm. Other manifestations of ADRs included hyponatremia, hypertension, difficulty urinating, excessive sweating, and jaw pain. The incidence of ADRs in the Itra and Vori groups was significantly higher compared with the Fluc and the control groups (P<0.05). In addition, the incidence of ADRs in the Itra group was significantly higher than that in the Vori group (P<0.05), whereas there was no significant difference in the incidence of ADRs between the Fluc and the control groups (P>0.05). Full and partial recovery from these ADRs occurred in 95.65% and 2.17% of cases, respectively, after the triazoles were discontinued. Death occurred in 2.8% of cases.

Discussion

VCR is one of the main drugs for the treatment of acute lymphoblastic leukemia (ALL) and lymphoid malignancies in children. The metabolism of vincristine is mainly mediated by the CYP superfamily and the P-gp transporter. The CYP superfamily is a class of monooxygenases primarily located in the endoplasmic reticulum of cells, which is responsible for most drug metabolism in humans. The superfamily is divided into several subfamilies, including CYP3A4, CYP3A5, CYP2D6, CYP2C9, and CYP2C19. Of these, CYP3A4 is the most abundant CYP isoenzyme in the small intestine and in the liver [11], and accounts for over 50% of drug metabolism [12]. Despite its low

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Table 3. ADRs between triazole AFDs and VCR.

	Different AFD groups			Total (n=92)	Control (n=44)
	Itra group (n=44)	Fluc group (n=42)	Vori group (n=6)		
Total number of ADRs cases	44 (100%)[a]	11 (26.19%)[b]	4 (66.67%)[a]	59 (64.13%)	13 (29.55%)
Gastrointestinal toxicity	38 (86.36%)	6 (14.29%)	1 (16.67%)	45 (48.91%)	5 (11.36%)
Constipation/Abdominal pain	38 (86.36%)	5 (11.90%)	1 (16.67%)	44 (47.83%)	5 (11.36%)
Vomiting	24 (54.54%)	1 (2.38%)	0	25 (27.17%)	0
Ileus	34 (77.27%)	0	0	34 (36.96%)	0
Perforation	1 (2.27%)	0	0	1 (1.09%)	0
Hepatitis	33 (75.00%)	0	0	33 (35.87%)	0
Electrolyte abnormalities	23 (52.27%)	0	0	23 (25.00%)	0
Autonomic neuropathy	21 (47.72%)	0	0	21 (22.83%)	0
Hypertension	8 (18.18%)	0	0	8 (8.70%)	0
Difficulty urinating	5 (11.36%)	0	0	5 (5.43%)	0
Excessive sweating	19 (43.18%)	0	0	19 (20.65%)	0
Peripheral neuropathy	26 (50.09%)	1 (2.38%)	2 (33.33%)	29 (31.52%)	0
Back pain	14 (31.81%)	1 (2.38%)	1 (16.67%)	16 (17.39%)	0
Arthralgia	8 (18.18%)	0	1 (16.67%)	9 (9.78%)	0
Limb weakness	12 (27.27%)	0	1 (16.67%)	13 (14.13%)	0
Muscle spasm	4 (9.09%)	0	0	4 (4.35%)	0
Cranial neuropathy	13 (29.54%)	0	0	13 (14.13%)	0
Transient visual loss	2 (4.54%)	0	0	2 (2.17%)	0
Jaw pain	7 (15.91%)	0	0	7 (7.61%)	0
Ptosis	4 (9.09%)	0	0	4 (4.35%)	0
Seizure	8 (18.18%)	0	0	8 (8.70%)	0
Time from first VCR dose to ADRs, median days (range)	8.5 (6–14)	18.9 (15–22)*	9.2 (5–16)	10.1 (4–22)	20.8 (17–23)
The number of VCR doses prior to ADRs	2 (1–3)	3 (2–4)	2 (1–3)	2 (1–4)	3 (2–4)
Outcome of ADRs					
Full recovery	40 (90.91%)	42 (100%)	6 (100%)	88 (95.65)	44 (100%)
Partial recovery	2 (4.55%)	0	0	2 (2.17)	0
Death	2 (4.55%)	0	0	2 (2.17)	0

[a] Indicates a significant difference from all other groups (P<0.05); [b] indicates a significant difference from the other experimental groups (P<0.05), but an insignificant difference from the control group (P>0.05). * Indicates a significant difference from the other experimental groups (P<0.05), but an insignificant difference from the control group (P>0.05).

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toxicity to bone marrow, primary toxicity of VCR is neurotoxicity, which is dose-related and cumulative with repeated dosage [13]. Therefore, the metabolism of VCR by the CYP isoenzymes is important to prevent accumulation of the drug and its toxicity to the body.

Triazole AFDs interact with VCR by suppressing its metabolism through the CYP superfamily and the P-gp transporter [1,2]. It has been found that itraconazole is primarily an inhibitor of both CYP3A4 and P-gp [14,15] due to its structure of a long hydrophobic arylaliphatic side chain, resulting in elevated plasma levels of VCR and aggravated toxicity. In contrast, fluconazole and voriconazole inhibit the activities of CYP3A4, CYP2C9, and CYP2C19, without affecting the function of P-gp [14,15]. These 2 drugs share a common structure of a substituted isopropyl group. Scholz and Moriyama et al. confirmed that voriconazole has a much greater inhibitory effect on CYP2C19 compared with CYP3A4/CYP2C9, and thus interacts primarily with drugs that are metabolized through the CYP2C19 pathway [16,17]. Fluconazole is a weaker inhibitor of CYP3A4 than itraconazole and voriconazole, and it inhibits the activity of CYP3A4 in a dose-dependent manner [18]. As a result, conventional prophylactic doses of fluconazole may not induce ADRs in patients treated with vincristine. To date, there are few case reports on the ADRs between fluconazole and VCR [19–21]. In this study, ADRs occurred much more frequently in the Itra and Vori groups compared with the Fluc and the control groups ($P<0.05$). Furthermore, the incidence of ADRs in the Itra group was significantly higher than that in the Vori group ($P<0.05$), whereas there was no significant difference in the incidence of ADRs between the Fluc and the control groups ($P>0.05$). Our results were generally consistent with the pharmacological findings described above, although the result for voriconazole might be inaccurate due to the small number of cases in the Vori group and needs to be verified in further studies. Therefore, fluconazole can be used as a preventive antifungal drug during VCR chemotherapy. However, with the increasing incidence of fluconazole-resistant isolates [22], more in-depth studies should be performed to identify better antifungal drugs.

It has been previously reported that the toxicity of VCR is potentially determined by the cumulative doses of the drug [13]. Higher previous doses of VCR might potentially lead to more severe and frequent toxicity following an adverse reaction with an AFD [4,10,23,24]. In this study, the incidence of ADRs in the Itra and Vori groups was significantly higher compared with the Fluc and the control groups ($P<0.05$), whereas the median number of VCR doses administered before the onset of ADRs was 2, 3, 2, 3 doses in the Itra, Fluc, Vori, and control groups, respectively, revealing no correlation between the cumulative doses of VCR and higher toxicity of the drug. However, further research shall be conducted on a larger number of cases to verify our observation.

In this study, a wide range of ADRs between VCR and triazole AFDs were reported, including gastrointestinal toxicity (48.91%), peripheral neuropathy (31.52%), electrolyte abnormalities (25%), autonomic neuropathy (22.83%), cranial neuropathy (14.13%), and seizures (8.7%). Although toxicities between VCR and triazole AFDs have been previously reported [9,24,25], the current work is unique in that it analyzed in detail the frequency of each specific type of ADRs in a relatively large number of patients receiving the combination of VCR and triazole AFDs (Table 3). The top 2 major ADRs in this study were gastrointestinal disorder and neurotoxicity, which is consistent with previous studies [10]. Nevertheless, our results suggest that gastrointestinal disorder was the ADR with the highest incidence, which is in contrast with previous studies in which neurotoxicity was more frequent than other ADRs [10]. Such discrepancies might be related to different medication regimes, as well as individual differences among patients in different studies. A plausible alternative explanation for our finding might contained in a study by Renbarger et al., in which the neurotoxicity of VCR was potentially associated with the difference in the CYP isozyme-mediated VCR metabolism in different races [26]. However, more research is needed to verify our results since the metabolic pathways of VCR have not yet been elucidated in Chinese patients. It is worth noting that electrolyte abnormalities, which are a previously reported rare neuropathy associated with the combination of VCR and triazoles [2], occurred in 25% of cases. Although seizures are an uncommon complication of VCR chemotherapy, they occurred in nearly 9% of cases in this study. In addition, the incidence of uncommon ptosis was 4.35%.

Full recovery from the ADRs occurred in 95.65% of cases after the triazoles were discontinued. In previous reports [2], folinic acid, vitamin B6, and glutamine were used to eliminate the VCR-associated toxicity, but yielded no encouraging results [27]. Two patients in the Itra group experienced only a partial recovery. Although there has been no lethality reported so far, 2 children died in the Itra group, which should not be conclusively attributed to the adverse interaction between itraconazole and VCR. However, the use of itraconazole should be avoided if possible in patients receiving VCR chemotherapy, and ADRs should be closely monitored when the combination of itraconazole and VCR is inevitable.

Several strategies might be feasible for managing the ADRs between vincristine and triazole AFDs, including close monitoring of VCR drug level in the body, the use of alternative non-triazole drugs, such as echinocandin and amphotericin B, or withholding the triazole AFDs before VCR chemotherapy. However, substantial supportive data is still required to evaluate the safety and effectiveness of these approaches. With the development of drug formulations, VCR liposomes may provide another approach to avoid this serious drug interaction.

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Conclusions

In conclusion, with the increasing incidence of IFIs in children with ALL, it has become extremely important to choose an appropriate AFD for effective prevention and treatment of IFIs without causing serious drug interaction between AFD and the essential chemotherapy agent VCR. The ADRs of the combination of VCR and triazole AFDs should be strictly monitored and treated in a timely manner to prevent serious and potentially life-threatening consequences.

References:

1. Chan JD: Pharmacokinetic drug interactions of vinca alkaloids: summary of case reports. Pharmacotherapy, 1998; 18: 1304–7
2. Moore A, Pinkerton R: Vincristine: can its therapeutic index be enhanced? Pediatr Blood Cancer, 2009; 53: 1180–87
3. Sathiapalan RK, Al-Nasser A, El-Solh H et al: Vincristine-itraconazole interaction: cause for increasing concern. J Pediatr Hematol Oncol, 2002; 24: 591
4. Ariffin H, Omar KZ, Ang EL, Shekhar K: Severe vincristine neurotoxicity with concomitant use of itraconazole. J Paediatr Child Health, 2003; 39: 638–39
5. Taflin C, Izzedine H, Launay-Vacher V et al: Vincristine induced severe SIADH: potentiation with itraconazole. Cancer Ther, 2004; 2: 149–51
6. Bermudez M, Fuster JL, Llinares E, Galera A, Gonzalez C: Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. J Pediatr Hematol Oncol, 2005; 27: 389–92
7. Takahashi N, Kameoka Y, Yamanaka Y et al: Itraconazole oral solution enhanced vincristine neurotoxicity in five patients with malignant lymphoma. Intern Med, 2008; 47: 651–53
8. Porter CC, Carver AE, Albano EA: Vincristine induced peripheral neuropathy potentiated by voriconazole in a patient with previously undiagnosed CMT1X. Pediatr Blood Cancer, 2009; 52: 298–300
9. Pana ZD, Roilides E: Risk of azole-enhanced vincristine neurotoxicity in pediatric patients with hematological malignancies: Old problem – New Dilemma. Pediatr Blood Cancer, 2011; 57: 30–35
10. Moriyama B, Henning SA, Leung J et al: Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses, 2012; 55(4): 290–97
11. Michalets EL: Update: Clinically significant cytochrome P-450 drug interactions. Pharmacotherapy, 1998; 18(1): 84–112
12. Prybys KM: Deadly drug interactions in emergency medicine. Emerg Med Clin North Am, 2004; 22: 845–63
13. Schiavetti A, Frascarelli M, Uccini S, Novelli A: Vincristine neuropathy: neurophysiological and genetic studies in a case of Wilms tumor. Pediatr Blood Cancer, 2004; 43: 606–9
14. Gubbins PO, Heldenbrand S: Clinically relevant drug interactions of current antifungal agents. Mycoses, 2010; 53: 95–113
15. Bruggemann RJ, Alffenaar JW, Blijlevens NM et al: Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis, 2009; 48: 1441–58
16. Scholz I, Oberwittler H, Riedel KD et al: Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. Br J Clin Pharmacol, 2009; 68: 906–15
17. Moriyama B, Falade-Nwulia O, Leung J et al: Prolonged half-life of voriconazole in a CYP2C19 homozygous poor metabolizer receiving vincristine chemotherapy: avoiding a serious adverse drug interaction. Mycoses, 2011; 54: e877–79
18. Dodds-Ashley E: Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy, 2010; 30: 842–54
19. Van Schie RM, Bruggemann RJ, Hoogerbrugge PM, Te Loo DM: Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother, 2011; 66: 1853–56
20. Harnicar S, Adel N, Jurcic J: Modification of vincristine dosing during concomitant azole therapy in adult acute lymphoblastic leukemia patients. J Oncol Pharm Pract, 2009; 15: 175–82
21. Lee JW, Seibel NL, Amantea M et al: Safety and pharmacokinetics of fluconazole in children with neoplastic diseases. J Pediatr, 1992; 120: 987–93
22. Pfaller MA, Castanheira M, Lockhart SR et al: Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of *Candida glabrata*. J Clin Microbiol, 2012; 50(4): 1199–203
23. Jeng M, Feusner J: Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukaemia. Pediatr Hematol Oncol, 2001; 18: 137–42
24. Kamaluddin M, Mc Nally P, Breatnach F et al: Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. Acta Paediatr, 2001; 90: 1204–7
25. Sathiapalan RK, El-Solh H: Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. Pediatr Hematol Oncol, 2001; 18: 543–46
26. Renbarger JL, McCammack KC, Rouse CE, Hall SD: Effect of race on vincristine- associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. Pediatr Blood Cancer, 2008; 50: 769–71
27. Mokhtar GM, Shaaban SY, Elbarbary NS, Fayed WA: A trial to assess the efficacy of glutamic acid in prevention of vincristine-induced neurotoxicity in pediatric malignancies: A pilot study. J Pediatr Hematol Oncol, 2010; 32: 594–600

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