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Citation	The 6th Medical Research Conference, Hong Kong, China, 13-14 January 2001, v. 23 n. 2 Supp, p. 52
Issued Date	2001
URL	http://hdl.handle.net/10722/54136
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S-HM-9

Clinical Characteristics and Risk Factors of Herpes Zoster after Bone Marrow Transplantation

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Introduction: Varicella Zoster virus (VZV) reactivation is common after BMT and is a cause of morbidity and repeated hospitalization. We reviewed the clinical characteristics and risk factors of VZV infection in BMT patients with a view of defining the optimal prophylactic strategy in this group of patients.

Patients and Methods: We retrospectively analysed 194 patients who underwent BMT from Jan 1997 to July 2000 in Queen Mary Hospital. VZV serology of patients and donors were determined before transplantation by ELISA methods. Patients receiving autologous transplants or BMT from HLA-identical siblings were given acyclovir as prophylaxis from conditioning until marrow engraftment against herpes simplex infection. Patients receiving BMT from matched-unrelated donors (MUD) and parents were given high dose acyclovir from conditioning until engraftment followed by ganciclovir three times a week until day 120, for prophylaxis against cytomegalovirus infection (CMV). All allogeneic BMT patients received prophylaxis against graft-versus-host disease (GVHD) comprising cyclosporin A and a short course of methotrexate. Herpes zoster was diagnosed clinically based on the presence of vesicular rash that was distributed along dermatome(s). Treatment included intravenous acyclovir (10 mg/kg every 8 hours) for five to seven days followed by oral valacyclovir (1 g thrice a day) or oral acyclovir (800 mg 5 times a day) for one week.

Results: Forty-four patients (23%) developed herpes zoster (HZ). The median time of infection was seven months post BMT (range: 2 to 33 months). Allogeneic BMT patients were at increased risk of HZ and those who received transplants from VZV naïve donors appeared to be at further risk of HZ compared with those from VZV immune donors. Ganciclovir given from marrow engraftment to day 120 post BMT did not reduce the overall incidence of HZ. Other factors, including age, the use of total body irradiation (TBI) and the development of chronic GVHD had no significant association with the occurrence of HZ.

Conclusion: Allogeneic BMT is a significant risk factor when compared with the autologous counterparts and BMT from VZV-positive donors might confer immunity to HZ after transplantation.

S-HM-10

Genetic Polymorphism at Exon 4 of Cytochrome P450 CYP2C9 in Chinese Patients might Determine the Warfarin Dose Requirement

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Background: Chinese patients generally require lower warfarin doses than Caucasians to maintain comparable anticoagulation but the reasons remain unknown. Cytochrome P450 2C9, the metabolizing enzyme of warfarin, has been shown to exhibit genetic polymorphisms at $C_{416}GT$ to TGT (Arg_{144} to Cys) in exon 3 and $A_{1061}TT$ to CTT (Ile_{359} to Leu) in exon 7, leading to impaired enzymatic activity and increased warfarin sensitivity. These polymorphic alleles, however, are rare among Chinese patients. We hypothesize that alternative polymorphic alleles might exist in this population accounting for the ethnic difference in drug disposition. **Methods:** Seventy-six Chinese patients receiving warfarin after prosthetic valve replacement were recruited. All patients have been given dietary advice to avoid interference with warfarin and those with severe congestive heart failure, liver cirrhosis and fluctuating warfarin dose requirement (≥ two times baseline) in the recent three follow-ups were excluded. Genetic analysis of CYP 2C9 was performed in 37 patients. DNA was extracted from buffy coat from 10 ml of citrated blood in each patient. Target sequences in CYP2C9 was amplified using primers specific for exons 1, 4 and 5 and PCR products were subjected to automated DNA sequencing. **Results:** The warfarin dose requirement in our patients ranged from 1.0 to 7.0 mg/day (Median 3.0 mg/day). Genetic analysis showed that exon 1 and 5 of cytochrome P450 2C9 did not exhibit polymorphism and the DNA sequences were identical to those in published cDNAs. The amplified sequence in exon 4 demonstrated single nucleotide alteration at four positions. The variants $CA_{561}G$ to CCG (Gln_{192} to His) $A_{527}TT$ to CTT (Ile_{181} to Leu) and $CA_{537}T$ to CCT (His_{184} to Pro) existed as heterozygotes at frequencies of 0.27, 0.22 and 0.19 respectively. Five patients (Frequency=0.14) were homozygotes of the $T_{608}TG$ to GTG (Leu_{208} toVal) alleles and they had a significantly lower warfarin dose requirement than those who were heterozygotes (N=27, Frequency=0.73) or homozygotes of the Leu_{208} alleles (N=5) (Mann-Whitney Test, $p<0.05$). **Conclusion** Chinese patients exhibited genetic polymorphism of CYP2C9 at four positions at exon four and the Leu_{208} to Val variants was associated with a lower warfarin dose requirement suggesting a genotypic-phenotypic association.