with β^0/β^0-thalassemia and co-inheritance of a single α-globin gene deletion all showed the β-thalassemia major phenotype, while β^0/β^+-thalassemia and co-inheritance of a single α-globin gene deletion, observed in only one patient, was associated with a β-thalassemia intermedia phenotype.

Our results show that co-inheritance of the SEA deletion ameliorates the clinical phenotype of β^0/β^+ but not necessarily that of β^0/β^0-thalassemia in Chinese patients with severe β-thalassemia. However, no definite conclusion is warranted about the phenotypic effect of a single α-globin gene deletion in view of the many fewer cases than the SEA deletion. This conclusion has two clinical implications. First, we propose that the presence of SEA deletion should be routinely determined in couples at risk of conceiving a fetus affected by β^0/β^+-thalassemia (i.e. parents who are discordant carriers of β^0- and β^+-thalassemia mutations), so that this information may be incorporated into the genetic counseling of such couples. Based on prevalence figures of β-thalassemia alleles[10] and assuming 70,000 live births annually, this amounts to eight pregnancies ($0.004 \times 0.027 \times 70{,}000$) per year. As Hb H inclusion bodies are typically absent in subjects who are heterozygous for both β-thalassemia mutation and SEA deletion, the presence of SEA deletion must be detected by PCR-based techniques.[10] Second, at prenatal diagnosis, a genotype of β^0/β^+-thalassemia and SEA deletion for the fetus is predictive of β-thalassemia intermedia, whereas the same cannot be said for compound heterozygous β^0/β^+-thalassemia only or β^0/β^0-thalassemia in association with SEA deletion.

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Key words: SEA deletion, α-thalassemia, β-thalassemia, thalassemia intermedia, genotype-phenotype correlation.

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Clinical characteristics of and risk factors for herpes zoster after hematopoietic stem cell transplantation

One hundred and eighty-three varicella-zoster virus seropositive patients after stem cell transplantation were reviewed. Herpes zoster developed in 41 patients (22.4%), at a median of seven (2-33) months post-transplantation. Stem cell transplantation from an allogeneic donor was the most significant risk factor (p<0.01) for the development of herpes zoster.

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Herpes zoster (HZ) occurs in 17-52% of patients after hematopoietic stem cell transplantation (SCT).[1] Most patients are seropositive for varicella zoster virus (VZV), indicating past infections. Despite treatment with high dose acyclovir, most patients suffer from complications including post-herpetic neuralgia, corneal ulceration, superimposed bacterial infection and viral dissemination.[2] We evaluated the clinical characteristics of HZ in a cohort of SCT patients treated at a single center, with a view to defining the clinical characteristics of and risk factors for this post-transplantation complication.

One hundred and ninety-four consecutive adult patients undergoing SCT in the Queen Mary Hospital and surviving more than two months were reviewed. Eleven patients were seronegative for VZV at transplantation and were excluded from subsequent analysis. The demographic characteristics of the remaining 183 patients are shown in Table 1. Acyclovir (5 mg/kg every 8 hours, conditioning to day 30) for prophylaxis against herpes simplex infection was used in autologous and allogeneic SCT from HLA identical siblings. In SCT from matched unrelated donors (MUD), high dose acyclovir (10 mg/kg every 8 hours) was given from conditioning to engraftment, followed by ganciclovir (5 mg/kg) three times a week until day 120, for prophylaxis against cytomegalovirus (CMV) infection. Pre-emptive ganciclovir was administered, when two consecutive polymerase chain reactions (PCR) for CMV were positive, to 6/55 autologous and 68/125 allogeneic SCT recipients. The duration of ganciclovir therapy, however, was subject to the discretion of the attending physicians and therefore not included in the analysis. HZ was defined clinically as the presence of a vesicular rash over one or more dermatomes. Treatment comprised high dose intravenous acyclovir (10 mg/kg every 8 hours) for 5-7 days followed by oral acyclovir (800 mg five times per day) or valacyclovir (1

Table 1. Clinical characteristics of 183 SCT* recipients with or without herpes zoster.

	No herpes zoster	*Herpes zoster*
Number of patients	142	41
Median age (years)	38 (17-67)	37 (17-63)
Male:female	74:68	28:13
Underlying diseases		
CML	38	13
AML	41	9
NHL	27	9
ALL	9	6
Others	27	4
Duration of follow-up (months)	11.0 (2-43)	15.0 (3-41)
VZV serology of patients		
Positive	139	39
Not available	3	2
Source of SCT		
Autologous	49	6
Twin	3	0
Sibling	76	30
Parent	1	0
MUD	13	5
Conditioning regimen		
TBI-containing	30	12
Chronic GVHD		
Yes	19	12
No	65	23
Not available/applicable	58	6

**There were 125 allogeneic SCT (106 from HLA-identical siblings, one from a parent, and 18 from matched unrelated donors, MUD), 55 autologous SCT, and three transplantations from monozygotic twins. CML : chronic myeloid leukemia; AML : acute myeloid leukemia; NHL : non-Hodgkin's lymphoma; ALL : acute lymphoblastic leukemia; VZV : varicella zoster virus, MUD : matched unrelated donor; TBI : total body irradiation.*

Table 2. Clinical characteristics of SCT recipients with herpes zoster.

Number of patients	41
Onset of HZ (time from SCT in months)	7 (2-33)
Distribution of HZ	
Trigeminal	8
Cervical	11
Thoracic	12
Lumbar	4
Sacral	2
Disseminated	4
Immunosuppression at presentation	
Yes	21
No	14
Autologous	6

g three times daily) for one week. The probability of developing HZ was evaluated by the method of Kaplan and Meier. Comparison between groups of data was made using the log-rank test. Contributions by different parameters to the occurrence of HZ were evaluated by multivariate analysis. A p value less than 0.05 was considered statistically significant.

Forty-one (22.4 %) patients developed HZ at a median of seven months post-SCT (Table 2). No patient developed HZ during acyclovir/ganciclovir prophylaxis or during pre-emptive ganciclovir therapy. Four patients presented with cutaneous dissemination and one patient had recurrent HZ in different dermatomes. None presented with visceral or central nervous system infection. There were no deaths. The risk of HZ was significantly higher after allogeneic SCT than after an autologous transplant (27.3% vs 11.0%, log-rank test p=0.007) and the HZ tended to be of later onset following an allogeneic SCT (median 7.0 vs 4.7 months), although this did not reach statistical significance (Mann-Whitney test, p>0.05). Whether the allogeneic SCT was from a sibling donor or MUD made no difference. Seven patients received SCT from VZV-seronegative donors. Three patients developed HZ. Three other patients died within eight months of SCT, so that the risk of HZ could not be ascertained. The age, underlying disease, use of TBI in the conditioning regimen and the development of GVHD, were not significantly associated with the development of HZ (log-rank test, $p > 0.05$).

Meta-analyses of data from groups of centers showed that autologous and allogeneic SCT carried comparable risks of HZ,[1] but data from single centers are scarce.[2-4] In this cohort of patients, we showed that allogeneic recipients had a significantly greater risk of HZ than autologous SCT recipients. This might be related to the delayed reconstitution of cellular immunity and increased immunosuppression after allogeneic SCT.[5-7] Most cases of HZ in this study were dermatomal in distribution with no systemic involvement, so that the outcome was more favorable than that reported from previous studies which included patients with significant VZV complications and fatalities.[3] However, whether the severity of dermatomal zoster (extent of skin involvement, severity of post-herpetic neuralgia), differs between allogeneic and autologus SCT recipients will have to be investigated further. We also report that 3/7 recipients of allogeneic SCT from VZV seronegative donors developed HZ. As the number of patients was small, the issue of whether VZV-specific T-cells from immune donors might be transferable and thus protective against HZ requires further investigation. Other factors, including the type of SCT, GVHD, age and the use of TBI, were not significant in VZV reactivation in this study.

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Polymerase chain reaction-based "pre-emptive" therapy with cidofovir for cytomegalovirus reactivation in allogeneic hematopoietic stem cells transplantation recipients: a prospective study

We prospectively evaluated the efficacy of the antiviral drug, cidofovir, as a pre-emptive therapy for cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation. Cidofovir was effective in 57% of cases without significant toxicity; response was inversely related to CMV DNA copy number at diagnosis. Cidofovir may represent a first-line therapy with some advantages over other commonly used drugs.

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Cytomegalovirus (CMV) infection remains the most frequent infectious complication after allogeneic hematopoietic stem cell transplantation (HSCT).[1] Pre-emptive therapy with ganciclovir and foscavir, especially if based on quantitative polymerase chain reaction (PCR) assays, reduces the risk of progression to CMV disease;[2,3] however, ganciclovir-induced neutropenia represents an independent risk factor for mortality,[4] while foscarnet causes renal toxicity.[5]

The nucleotide analog cidofovir has recently been licensed for treatment of CMV retinitis in patients with acquired immunedeficiency syndrome (AIDS); it is also active on adenoviruses and polyomaviruses, and its pharmacokinetic profile allows a once-a-week administration.[6] To evaluate the efficacy of cidofovir as a PCR-based pre-emptive therapy in HSCT recipients, we enrolled 56 consecutive patients in a prospective study; in 14 of these who showed CMV reactivation, therapy with cidofovir was instituted. The PCR assays for CMV DNA in plasma and whole blood samples were performed with a commercially available kit (CMV-Ibridoquant Kit; Bioline Diag., Turin, Italy), twice weekly from day +15 to +30, then weekly up to day +120. Patients positive (CMV genome copy number ≥100/mL of blood and ≥500/mL of plasma) in two consecutive assays received cidofovir as first-line pre-emptive therapy, with a shift to ganciclovir ± foscavir in case of therapy failure. Cidofovir was administered at a dose of 5 mg/kg weekly for two weeks followed by two doses (3 mg/kg) every other week. Patients received oral probenecid (2 g three hours before therapy, and 1 g two and eight hours after the end of the cidofovir infusion) and pre-hydration (2,000 mL); creatinine levels and proteinuria were monitored weekly. No other antiviral therapy was allowed concurrently with cidofovir, while all patients had received prophylaxis with intravenous acyclovir (500 mg/m^2/three times a day from day –5 to day +30).

Table 1. Characteristics of the 14 patients who entered the study.

Age median (range,years)	41 (24-59)
Time from HSCT to CMV reactivation (days)	46 (21-97)
Diagnosis	
Acute myeloid leukemia	7
Acute lymphoid leukemia	2
Chronic myeloid leukemia	3
Multiple myeloma	2
Donor type	
HLA-identical sibling	9
Matched unrelated	4
Partially-matched (4/6) cord blood	1
Conditioning regimen	
TBI + Cy	9
CT	
CMV status of donor (D) and recipient (R)	5
D-/R+	3
D+/R+	11
Pancytopenia	14
Acute graft-versus-host disease	6

TBI, hyperfractioned total body irradiation (1320 cGy); Cy, cyclophosphamide; CT, other chemotherapy-only regimens. Pancytopenia= neutrophils < 10^9/L and/or platelets < 50×10^{12}/L.

Table 2. Changes in CMV DNA copy numbers during cidofovir treatment in the 8 patients who responded to the treatment.

CMV DNA copies (percent reduction after)	*Blood*	*Plasma*
First dose	53±22%	2±1
Second dose	79±19%	93±3
Third dose*	97±3%	99±1

Values reported are expressed as the percent reduction (± SD) taking the value recorded at diagnosis, just before starting cidofovir treatment, as 100%.
**Only 3 patients received a fourth dose.*

The outcome of cidofovir therapy was defined as: *response*, negativization of PCR test; *failure*, persistence of PCR positivity after 2 doses, or progression after any dose of cidofovir as shown by an increase in DNA blood levels or a positive test for CMV pp65; *toxicity*, a >1.5-fold increase in serum creatinine levels or development of proteinuria.

Reactivation of CMV occurred in 14/56 patients at a median of 46 days (range, 21-97) after HSCT; in all cases it was associated with pancytopenia and in 6 with acute graft-versus-host disease (grade II-III) under steroid treatment (Table 1). Virus clearance was obtained in 8/14 patients (57%), in half of whom after two doses of cidofovir; all became pp65 negative. Table 2, which reports the percentage changes in DNA copy number along with treatment, shows that an almost complete clearance was obtained after the second dose. The mean number of CMV DNA copies in plasma at diagnosis was lower in responders