BRIEF REPORT
Varicella Zoster Immune Status in Children Treated for Acute Leukemia

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INTRODUCTION
Varicella zoster virus (VZV) is a human alphaherpesvirus, which causes Varicella (chicken pox) as the primary infection. As with other alphaherpesviruses VZV establishes latency and reactivates to cause Herpes zoster (shingles). VZV is lymphotropic (for CD4 and CD8 lymphocytes) and also induces production of cytotoxic T cells that recognize and destroy virus-infected cells [1]. Varicella in lymphopenic individuals however, can result in severe disease with increased risk of dissemination and death [2,3].

Leukemia is the most common form of childhood malignancy; acute lymphoblastic leukemia (ALL) represents about 80% of cases, acute myeloid leukemia (AML) about 15% [4]. Both the disease and the treatment are immune suppressive; leukemia has an effect on the adaptive immune system [5,6], and chemotherapy causes reductions of B-lymphocyte [7], T-lymphocyte [8] and total immunoglobulin (Ig) levels [6,9]. B- and T-lymphocyte function usually recovers by 6 months after completion of chemotherapy, although this may take up to 1 year [7,8]. As a result of this immune suppression, particularly the T-cell lymphopenia and poor T cell function, children treated for acute leukemia are at increased risk of severe varicella and zoster [2,3,10]. Steroid therapy as part of the treatment regimen for acute leukemia can further increase the severity of varicella in these children [11]. To prevent varicella related morbidity and mortality susceptible individuals require post-exposure prophylaxis (PEP) in the form of acyclovir and/or VZV specific immunoglobulin G (VZIG) [12,13]. For those that develop varicella the temporary suspension of chemotherapy, and antiviral treatment is recommended to reduce morbidity and mortality [13,14].

VZV vaccination is not routine in the United Kingdom (UK) and is not recommended for immune compromised children [12,13]. Thus, more children are likely to be susceptible to varicella in the UK compared to countries where VZV vaccine is routinely given. Additionally, the immunosuppressive therapy given for acute leukemia can result in loss of previously established immunity, this has been demonstrated for vaccine antigens [15,16]. A UK based report has shown that children who were VZV immunoglobulin G (VZV IgG) positive at the start of chemotherapy for ALL went on to develop varicella during treatment [17]. This suggests that loss of VZV IgG during treatment can be associated with a risk of VZV reinfection [17].

We studied the VZV sero-status of children prior to starting chemotherapy and after completion of chemotherapy for acute leukemia.

METHODS
Patient Population
The study was conducted over a 2-year period, from 1st October 2002 to 30th September 2004. Patients were recruited from the Paediatric Department at The Royal Marsden Hospital (RMH), Sutton, UK. Patients were recruited as part of a re-vaccination study that entailed measurement of specific antibody concentrations against vaccine preventable infections. Eligible patients were aged 1–18 years, diagnosed with ALL or AML and starting chemotherapy according to the Medical Research Council of United Kingdom ALL (MRC UKALL97 modified UKALL99, and for disease relapsed patients UKALL R2) and UKAML (UKAML10 or UKAML12) protocols.

Informed consent was obtained from the patient or their parent, by the provision of information sheets for parents and age appropriate ones for children. The RMH ethics committee approved the study.

Clinical data on each patient were obtained from the RMH electronic-patient records. Blood (5–10 ml) was obtained for serological testing. Blood was centrifuged and serum was separated and frozen in aliquots at −20°C on the same day, until tested in batches.

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Antibody Assay

Recruited patients had their VZV serostatus checked using time resolved fluorescence immunoassay (TRFIA) before starting treatment and again at least 6 months after completion of treatment. The cutoff for a positive TRFIA is >150 mIU/ml, a level which from mixture modeling best distinguishes between populations with and without VZV specific IgG and used as a surrogate marker of protection [18]. A VZV IgG level <100 mIU/ml equates to susceptibility to infection and a level between 100 and <150 mIU/ml is reported as equivocal [18]. In this study we considered all equivocal results as negative, which increased assay specificity.

RESULTS

Pre- and post-treatment VZV serology results were available for 52 and 26 patients, respectively. Post-treatment samples were obtained at a median time of 0.67 years (quartile, 0.5–0.96) after completion of treatment. Median age of patients pre-treatment was 5.25 years (range 1.08–14.25) and median age of patients at time of serological testing was 7.96 years (range 2.75–18). There was no significant difference in age between patients treated for ALL and AML.

Pre-treatment, 35% (18/52) were VZV seronegative and post-treatment 38% (10/26) were VZV seronegative. Paired sera were available for 26 cases (20 ALL patients, 6 AML patients). Of the paired samples, 35% (9/26) and 38% (10/26) were seronegative pre-treatment and post-treatment, respectively: 11 remained positive (3 AML, 8 ALL), 2 remained negative (1 AML, 1 ALL), 1 changed from positive to negative (ALL), 5 from positive to equivocal (2 AML, 3 ALL), 3 from negative to positive (ALL), and 4 from equivocal to positive or negative (Fig. 1). Equivocal result were considered negative, thus, overall VZV antibody concentrations decreased during treatment in six patients (four ALL, two AML) to a level considered non-protective, and VZV antibody concentrations increased in three patients (all ALL) to a level considered protective.

Patients did not receive intravenous immunoglobulin (IVIG) or VZIG within 3 months of serological analysis after completion of treatment; however, we do not have information outside this period. We do not have information on VZV vaccination status of family members; however, we know that family members were not offered VZV vaccination at the study center.

DISCUSSION

Prevention of varicella in children with cancer is important in view of the associated morbidity and mortality [2,3]. Our study demonstrated that 35% of patients with acute leukemia were VZV seronegative and susceptible to varicella prior to starting chemotherapy. This group of patients will need PEP on exposure to VZV [12,13], and should they develop varicella would require intravenous antiviral therapy [13,14]. Another UK based study demonstrated 24% of children treated for cancer were seronegative for VZV and 250 children/year required PEP [19].

On completion of treatment for acute leukemia 65% (11/17) maintained VZV immunity. While 35% (6/17) became seronegative; this loss of protective antibody can be associated with susceptibility to varicella re-infection [17]. This highlights the importance of checking VZV serostatus on exposure irrespective of serostatus prior to starting treatment. If VZV serostatus is not checked at the time of VZV exposure it could result in wrongly giving PEP, or more worryingly, not giving PEP in cases where it is needed.

VZV vaccination is not routine in the UK and it is not recommended for immune compromised children. It is, however, recommended for VZV susceptible household members of children receiving cancer treatment [12,13], although compliance with this recommendation appears to be low [19]. VZV vaccination during the maintenance phase of treatment has also been shown to be safe and effective [20]. Nevertheless, the best strategy for reducing exposure in these children is through universal vaccination of healthy children and this should reduce the incidence and associated complications of varicella in children treated for acute leukemia [21]. Until this is achieved the importance of minimizing exposure to VZV, timely identification of exposure, assessment of immune status and provision of PEP must be emphasized to patients and their families.

Fig. 1. VZV serology for paired serum samples before and after treatment for acute leukemia.
REFERENCES