Hematopoietic chimerism was analyzed in serial bone marrow samples taken from 28 children following T-cell depleted unrelated donor bone marrow transplants (UD BMT) for acute lymphoblastic leukemia (ALL). Chimeric status was determined by polymerase chain reaction (PCR) of simple tandem repeat (STR) sequences (maximal sensitivity, 0.1%). At least two serial samples were examined in 23 patients. Of these, two had evidence of complete donor engraftment at all times and eight showed stable low level mixed chimerism (MC) (<1% recipient hematopoiesis). All 10 of these patients remain in remission with a minimum follow-up of 24 months. By contrast, 13 patients demonstrated a progressive return of recipient hematopoiesis. Five of these relapsed (4 to 9 months post BMT), one died of cytomegalovirus pneumonitis and seven remain in remission with a minimum follow-up of 24 months. Five children were excluded from serial analysis as two serial samples were not collected before either relapse (3) or graft rejection (2). We conclude that as with sibling transplants, ex vivo T depleted UD BMT in children with ALL is associated with a high incidence of MC. Stable donor engraftment and low level MC always correlated with continued remission. However, detection of a progressive return of recipient cells did not universally correlate with relapse, but highlighted those patients at greatest risk. Serial chimerism analysis by PCR of STRs provides a rapid and simple screening technique for the detection of relapse and the identification of patients with progressive MC who might benefit from detailed molecular analysis for minimal residual disease following matched volunteer UD BMT for childhood ALL.

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THE INCIDENCE AND significance of mixed chimerism (MC) following bone marrow transplantation (BMT) for hematological disease has been investigated by several groups over the last decade.1 9 With the use of increasingly sensitive techniques for the detection of residual recipient cells, MC is frequently observed post allogeneic BMT. Various transplant and patient related factors have been associated with an increase in MC after sibling BMT. These reflect either a decrease in the number of allogeneic cells infused or less intense conditioning and include T-cell depletion,1,4,7,10,11 lower midline total body irradiation (TBI) dose,5,6,12 and younger patient age.12

More important than simple documentation of the incidence of MC is an assessment of its relevance in relation to clinical outcome, particularly any correlation with relapse. It is likely that this will vary according to the underlying disease and the conditioning regime used. For example, while mixed T-cell chimerism is associated with the persistence of minimal residual disease (MRD) and leukemia relapse after sibling BMT for chronic myeloid leukemia (CML),13 a similar correlation has not been found after sibling BMT for acute lymphoblastic leukemia (ALL).

In this study, we have investigated the incidence and clinical impact of persistent recipient hematopoiesis in serial samples taken from a large group of patients who have received similar conditioning therapy for the same disease in a single center. We wished to answer three main questions. First, is the incidence of MC following T-cell depleted unrelated donor (UD) BMT similar to that found after T-cell depleted sibling BMT? Second, is stable donor engraftment necessary for continued remission? Finally, could a relatively simple molecular technique for the detection of MC reliably predict relapse in this group of patients?

MATERIALS AND METHODS

Patients. Twenty-eight ALL patients, mean age 5.4 years (range, 0.75 to 16), were investigated in this study. All transplants were performed at Bristol Children’s Hospital between 1989 and 1993. One patient (UPN18) with Philadelphia positive ALL was transplanted in first remission. The remaining children were transplanted in second remission. HLA typing was performed by serology for Class 1 in all patients. Class 11 typing was initially performed by restriction fragment length polymorphism (RFLP) (20 patients) and later by intermediate resolution polymerase chain reaction (PCR) SSP (sequence specific PCR) (eight patients). High resolution molecular Class 11 typing was not undertaken. Nineteen donor/recipient pairs were deemed to be matched and nine mismatched (see Table 1). All grafts were T-cell depleted with Campath 1M14 ex vivo. Conditioning included in vivo T depletion of the recipient with CAMPATH-1G,14 cyclophosphamide (120 mg/kg) and total body irradiation (TBI). The total TBI dose was 14.4 Gy in eight fractions for all patients except UPN18 who received 10 Gy as a single fraction. All patients received cyclosprine (3 mg/kg total) as graft-versus-host disease (GVHD) prophylaxis until 3 months post-BMT. This was gradually discontinued between 3 and 6 months post-BMT in the absence of GVHD. An additional short course of methotrexate15 was given to those patients transplanted from mismatched donors after 1991.

Specimens. Bone marrow (BM) samples were collected from the donor and recipient before transplant and from the recipient at regular intervals from 1 to 36 months posttransplant. Genomic DNA was isolated from either fresh BM mononuclear cells or archival BM smear slides as described previously.16

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3027
**Table 1. Chimerism Post UD BMT for Childhood ALL**

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<td>M (50%)</td>
<td>M (50%)</td>
<td>0</td>
<td>CR</td>
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Time to relapse and duration of remission is given in months.

Abbreviations: UPN, unique patient number; M, mixed chimera; R, recipient cells; D, donor chimera; AR, autologous rescue; CHR, chronic; CR, complete remission; R2, second relapse; Trans, Chim, transfusion chimera; N/A, not available; mm, mismatched transplants.

* Detection limit.

**Simple tandem repeat (STR) analysis.** STRs (microsatellites) are di, tri, or tetra-nucleotide repeat sequences that are dispersed throughout the human genome. They are polymorphic in that the number of repeat units varies between individuals. Following amplification in the PCR, the length of fragment generated will be directly proportional to the number of repeat units present. This size difference may be discriminated following electrophoresis on high resolution polyacrylamide gels, thus allowing the identification of different individuals. The sensitivity of the microsatellite assay is below 1% in the detection of the minor cell population. The STR-PCR assay is a semiquantitative one with an error margin of ±5% in detecting minor cell populations above the 10% level. However, significant increases or decreases in donor or recipient cell populations can be determined by amplification of serial samples and, in our hands, comparable results were seen using different STR markers. Furthermore, all gels were independently read by two individuals.

**Oligonucleotide primers.** A panel of four microsatellite markers, vWF,17 ACPP,18 CYP19,19 and INT-220 was used in the initial screening process to identify a minimum of two markers polymorphic between a given donor/recipient pair. Once informative markers were defined, PCR amplification of posttransplant marrow samples was performed to estimate the degree of chimerism. As patient and donor were unrelated, markers of high polymorphism information content (PIC) values were found to be informative in all donor/recipient pairs in this study.

**PCR.** PCR was performed on 200 ng of DNA in a 25-μL reaction. The reaction mix consisted of 1× PCR buffer (10 mmol/L Tris·Cl (pH 8.3), 50 mmol/L KCl, 1 mmol/L MgCl₂, 1% Triton), 200 μmol/L each of deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dTTP), and deoxycytidine triphosphate (dCTP), 2 mmol/L deoxycytidine triphosphate (dCTP), 25 pmol/L of each primer, 0.5 U of DNA Taq polymerase and 0.1 μCi of alpha-32PdCTP. Primer sequences and cycling parameters have been published previously.21-23 All reactions were amplified on a Trioblock thermal cycler (Biometa, Germany) using the hot start method.

**Electrophoresis.** PCR products (2.5 μL) were combined with an equal volume of formamide loading buffer and electrophoresed on 8% denaturing polyacrylamide gels at 40 mA for 3.5 hours. Resulting gels were transferred to 3MM Whatman paper, dried down, and exposed to autoradiograph film.

**Definition of chimerism.** The patients were subdivided into three groups based on their chimeric status. Patients who showed no evidence of recipient cells at any time posttransplant were said to be donor chimeras. Secondly, patients who showed a persistent low level (<1%) of recipient cells in successive samples for a minimum of 9 months posttransplant were referred to as stable low-level mixed chimeras. Finally, the remaining patients displayed progressive mixed chimerism (PMC) showing either a change from donor to mixed chimerism or increasing mixed chimerism in serial BM samples.

**RESULTS**

**Donor chimerism.** Stable complete donor chimerism (DC) was observed in 2 patients (UPN 19 and 28), both of whom remain in remission 48 and 24 months post-BMT.
Chimerism and clinical course. Stable donor engraftment and low level MC in serial samples from 43% of the patient cohort correlated with continuous CR. However, no correlation could be made between clinical outcome and the evolution of PMC observed in the remaining 57% of patients.

Due to the low frequency of acute GVHD in this pediatric patient population, no significant correlation could be observed between the incidence of acute GVHD and the evolution of chimerism. Only two patients (UPN 16 and 30) were treated for greater than grade 2 GVHD. Both were recipients of mismatched grafts, and it is of note that both were complete donor chimeras at the onset of symptoms.

The low resolution tissue typing employed in these patients and the small number of mismatched transplants preclude any detailed analysis of the impact of HLA disparity on chimeric status. It is of note that all episodes of graft rejection and grade 2 or greater GVHD occurred in mismatched patients.

Discussion

Allogeneic BMT is the treatment of choice for a minority of children with high-risk ALL in first remission and for the majority of those who relapse. Barrett et al.25 recently provided evidence that BMT from HLA-identical siblings results in a statistically greater likelihood of leukemia-free survival at 5 years than does chemotherapy in children with ALL in second or subsequent CR. As only a third of patients have a suitable family donor, transplantation from unrelated mismatched donors is appropriate.26 With the use of single antigen mismatched donors, it is possible to find a donor for many children considered suitable for an allograft. However, unmanipulated (T-cell replete) unrelated donor transplant carries a 70% to 90% incidence of Grade 2 to 4 GVHD and

Low-level MC (<1%). Eight patients (UPN 2, 7, 9, 10, 12, 14, 25, and 27) demonstrated stable low-level MC for at least 9 months post-BMT. A representative example is shown in Fig 1. All of these patients remain in remission at least 24 months posttransplant. Eventual conversion to complete donor hematopoiesis (loss of detectable recipient band) occurred in five patients between 9 and 36 months posttransplant.

Progressive MC. Of the 13 patients who showed high or progressive MC, one patient (UPN 22) died at 4 months from CMV pneumonitis. MC had increased from <1% at 1 month post-BMT to 5% when death occurred. There was no evidence of clinical relapse at this time. Progressive mixed chimerism in the remaining 12 patients was not predictive of either relapse or disease-free survival (DFS). Increasing MC heralded relapse in five patients (UPN 1, 6, 15, 23, and 26) and partial autologous recovery in seven patients (UPN 3, 13, 16, 18, 24, 30, and 32). Of the five patients who relapsed, a change from DC to MC in the first 3 months post-BMT preceded clinical relapse in two patients (UPN 6 and 15). UPN 1 had persistence of relatively high levels of recipient hematopoiesis at all times analyzed, while UPN 23 and 26 showed increasing levels of recipient cells at least 1 month before relapse. UPN 23 relapsed at 5 months when the bone marrow showed 50% recipient cells (result not shown). He received further palliative chemotherapy with vincristine and prednisolone and entered morphological remission 6 months after BMT. Chimerism at this time indicated return of predominantly donor hematopoiesis. The remission was maintained with oral Mercaptopurine until 12 months post-BMT when he again relapsed and died.

Seven patients (UPN 3, 13, 16, 18, 24, 30, and 32) showing progressive MC remain in complete remission (CR) at an average of 30 months posttransplant (see Table 1 and example in Fig 2). Levels of recipient cells range from 10% to 65% and are apparently unstable. Three of these patients received transplants from sex mismatched donors and cytogenetic analysis also indicated progressive MC. For example, in UPN 30, who received a sex mismatched transplant from a female donor, STR-PCR analysis at 9 months indicated 60% recipient cells, while cytogenetic analysis detected 80% male cells; at 21 months the STR-PCR profile indicated 90% recipient cells, while cytogenetic analysis detected 97% male cells. In addition, donor cells in the sex matched transplant for UPN 3 had a marker chromosome 13 and cytogenetic and STR-PCR analysis yielded comparable results, eg, month 24, STR-PCR 20% recipient, cytogenetics 15.7% recipient; month 30, STR-PCR 25% recipient, cytogenetics 17% recipient. STR-PCR always detected MC at or before detection of recipient cells by cytogenetic analysis.

Chimerism and clinical course. Stable donor engraftment and low level MC in serial samples from 43% of the patient cohort correlated with continuous CR. However, no correlation could be made between clinical outcome and the evolution of PMC observed in the remaining 57% of patients.
significant (20% to 50%) transplant related mortality. For this reason, many groups routinely T-cell deplete unrelated donor grafts. In Bristol, over 50% of 56 children who received T-cell depleted UD BMT for ALL in second CR remain in remission (53% event-free survival [EFS] at 2 years). The procedural mortality in this cohort is 10%, and the major cause of death is relapse.

In this study, MC was documented at least once after transplant in 26 of 28 (93%) patients. The results are not significantly higher than those reported by other investigators after T-cell depleted sibling BMT, and the incidence of MC is significantly greater than that seen after unmanipulated sibling grafts. It is likely that this is directly related to the use of T-cell depletion and/or HLA matching of the donor and recipient, as these patients received standard dose cyclophosphamide and a high midline dose of TBI.

Documentation of the incidence of MC provides only limited information about its clinical impact. More useful data can be obtained from serial analyses that focus on a patient population with a single common hematologic disorder. All 10 patients who had evidence of stable donor engraftment (ie, complete donor or stable low-level MC) in serial samples remain in remission at least 18 months after transplant. Of interest, five patients with initial evidence of stable low-level MC converted to DC up to 36 months post-BMT. This differs from the findings of Roy et al and Mackinnon et al who found that no patient demonstrating MC after T-cell depleted sibling BMT subsequently converted to DC.

No correlation could be made between the evolution of progressive MC and clinical outcome in this study. Over 50% of those patients with evidence of PMC by STR-PCR and, in some cases by cytogenetic analysis, remain in remission. Although eventual relapse cannot be excluded in these patients, we believe that this is unlikely. All patients have been followed for at least 24 months and, in our experience, relapse following UD BMT for ALL, occurs within 12 months of transplant. The lack of a clear relationship between MC and relapse after BMT for ALL is in marked contrast to experience in CML. Roux et al speculated that the clinical impact of MC depends on the underlying disease and the influence of any graft-versus-leukemia effect in mediating remission after BMT. Our findings support this hypothesis and imply that the development of tolerance as indicated by MC is not necessarily associated with relapse after T-depleted UD BMT for ALL. With the proviso that ALL is a heterogeneous condition, we suggest that T-cell depletion is not likely to result in a higher rate of relapse than seen after unmanipulated UD BMT for ALL. This is supported by the very similar relapse rate seen after T-cell repleted UD BMT for childhood ALL and that seen in both the Bristol series and recent results from Wisconsin.

Finally, this study illustrates an important point about the early detection of relapse after allogeneic BMT for ALL. STR analysis potentially provides a simple method for early detection of relapse. However, it is not leukemia-specific aid, in this series, we demonstrated that detection of progressive MC, in unsorted marrow fractions does not uniformly correlate with the recurrence of leukemia. Therefore, this technique alone cannot be used to predict relapse. Rather, it can be employed to highlight a group of patients at greatest risk who would be candidates for more complex investigation of minimal residual disease (MRD). The most widely applicable and sensitive technique for the detection of MRD in ALL is gene rearrangement PCR, and we are now examining the correlation between chimeraism, MRD, and eventual relapse after UD BMT for ALL.

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residual disease is more common in patients who have mixed T-cell chimerism after bone marrow transplantation for chronic myelogenous leukemia. Blood 83:3409, 1994


Patterns of hematopoietic chimerism following bone marrow transplantation for childhood acute lymphoblastic leukemia from volunteer unrelated donors

K Molloy, N Goulden, M Lawler, J Cornish, A Oakhill, D Pamphilon, M Potter, C Steward, K Langlands, P Humphries and SR McCann

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