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Comparison of Chimerism and Minimal Residual Disease Monitoring for Relapse Prediction after Allogeneic Stem Cell Transplantation for Adult Acute Lymphoblastic Leukemia

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A B S T R A C T

Little data are available on the relative merits of chimerism and minimal residual disease (MRD) monitoring for relapse prediction after allogeneic hematopoietic stem cell transplantation (HCT). We performed a retrospective analysis of serial chimerism assessments in 101 adult HCT recipients with acute lymphoblastic leukemia (ALL) and of serial MRD assessments in a subgroup of 22 patients. All patients had received myeloablative conditioning. The cumulative incidence of relapse was significantly higher in the patients with increasing mixed chimerism (in-MC) compared with those with complete chimerism, low-level MC, and decreasing MC, but the sensitivity of in-MC detection with regard to relapse prediction was only modest. In contrast, MRD assessment was highly sensitive and specific. Patients with MRD positivity after HCT had the highest incidence of relapse among all prognostic groups analyzed. The median time from MRD positivity to relapse was longer than the median time from detection of in-MC, but in some cases in-MC preceded MRD positivity. We conclude that MRD assessment is a powerful prognostic tool that should be included in the routine post-transplantation monitoring of patients with ALL, but chimerism analysis may provide additional information in some cases. Integration of these tools and clinical judgment should allow optimal decision making with regard to post-transplantation therapeutic interventions.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) is a well-established postremission therapy in adults with acute lymphoblastic leukemia (ALL) with certain high-risk features [1,2]. Some protocols advocate HCT even in standard-risk ALL [3,4]. HCT is also applied in patients in second or higher complete remission (CR), and for selected patients with refractory disease. Although treatment-related mortality has declined in recent years, relapse remains a frequent cause of death after HCT, particularly in patients with advanced disease [5].

Salvage therapies for overt hematologic relapse after HCT are often futile [6], but intervention in early relapse when the leukemia burden is still low may be effective [7,8]. The 2 methods available for early relapse prediction are monitoring of minimal residual disease (MRD), by flow cytometry for leukemia-associated aberrant immunophenotypes or by real-time quantitative polymerase chain reaction (qPCR) for fusion genes or clonal immunoglobulin or T cell receptor (Ig/TCR) gene rearrangements [9-17], or sequential measurements of donor chimerism, primarily by fluorescence-based PCR amplification of short tandem repeat (STR) markers [18-22]. Whereas MRD directly detects residual or reemerging leukemia clones, chimerism analysis provides information only on the persistence or reemergence of autologous hematopoiesis. In addition, standard MRD assays usually have at least a 1 log greater sensitivity than assays used for the assessment of chimerism [18,23].

Both of these methods have been applied in the post-transplantation setting in adults with ALL [19], but their relative merits with regard to relapse prediction have not been thoroughly evaluated. The impact of chimerism has been analyzed primarily in pediatric ALL populations

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[8,19-21,24-27], in whom distinct immunologic mechanisms may exist [28]. MRD studies, although indicating an increased relapse risk in patients with MRD positivity after HCT [7,11,29-33], generally have not provided comparative data to chimerism. In this context, a recent National Cancer Institute workshop concluded that it is critically important to assess the clinical relevance of MRD and chimerism surveillance in individual diseases [19], and a recent evidence-based review on the role of HCT in adult ALL concluded that monitoring of MRD after allogeneic HCT is an area meriting further research [34].

Here we present a retrospective analysis of serial chimerism assessments in 101 adults with ALL, and of serial MRD assessments in a subgroup of 22 patients, all of whom had undergone myeloablative allogeneic HCT at our center between 1999 and 2009. We examined the kinetics of MRD and chimerism signals and evaluated whether either of these 2 methods provides better relapse prediction, potentially allowing for earlier and more successful therapeutic intervention.

PATIENTS AND METHODS

Patients

A total of 146 adults with ALL underwent allogeneic HCT at our center between 1999 and 2009. For the present study, patients who received reduced-intensity conditioning and/or underwent a second allogeneic HCT (n = 31), as well as patients for whom chimerism data were unavailable (owing to, eg, death before day 28 or follow-up at external centers [n = 14]), were excluded, leaving a final study population of 101 patients (Table 1). MRD data were available for a subgroup of 22 patients.

All patients were diagnosed and treated under the German Multicenter Study Group for Adult ALL (GMALL) study protocol 06/99 or 07/03 [1,35,36]. Patient-, disease-, and transplantation-related characteristics and follow-up information were recorded prospectively in an electronic database, and chimerism and MRD data, as well as data on the occurrence of graft-versus-host disease (GVHD), were gathered retrospectively from patient files by standardized medical record abstraction. All patients gave informed consent for analysis of their data, in accordance with the Declaration of Helsinki.

The patients were at high risk for relapse or progression and underwent transplantation in first CR (n = 59), in second CR or greater (n = 19), in active relapse (n = 21), or with primary refractory disease (n = 2) (Table 1).

Table 1
Patient and Treatment Characteristics

Characteristic	Value
Number of patients	101
Sex, %	
Male	64
Female	36
Age at HCT, yr, median (range)	33 (17-55)
Karnofsky Performance Status, %	
100	49
90	41
≤80	10
HCT-CI, %	
Low	28
Intermediate	46
High	27
Disease status at HCT, %	
CR1	58
CR2 or greater	19
No CR	23
Lineage, %	
B-ALL	71
T-ALL	29
Cytogenetic risk group, %	
Philadelphia chromosome positive	22
High risk [t(4;11), t(8;14), CA]	16
Other aberrations	16
Normal karyotype	47
Donor type, %	
Matched related donor	37
Matched unrelated donor	51
Mismatched donor	12
Stem cell source, %	
Peripheral blood stem cells	91
Bone marrow	9
ATG during conditioning, %	
Yes	29
No	71
DLI given, %	
Yes	38
No	62

CA indicates complex aberrant.
Percentages may not total 100% because of rounding.

Conditioning and GVHD Prophylaxis

Patients received myeloablative conditioning based on total body irradiation (TBI) 6 × 2 Gy, in combination with either cyclophosphamide 2 × 60 mg/kg (n = 60) or etoposide 1 × 60 mg/kg (n = 33), cyclophosphamide 2 × 50 mg/kg + etoposide 1 × 50 mg/kg (n = 5), or an alternative regimen without TBI based on treosulfan 3 × 12 g/m^2 + cyclophosphamide 2 × 60 mg/kg + etoposide 1 × 30 mg/kg (n = 2) or busulfan 4 × 4 mg/kg + cyclophosphamide 2 × 60 mg/kg (Table 1). GVHD prophylaxis consisted of cyclosporine A (CSA) combined with short-course methotrexate (n = 76), mycophenolate mofetil (n = 9), or prednisolone (n = 16). Antithymocyte globulin (ATG; Fresenius) 3 × 10 or 20 mg/kg/day was given initially only to patients with mismatched donors and then, starting in 2004, also in patients with a matched unrelated donor (n = 29).

Allogeneic Transplantation

HLA typing was performed by PCR sequence-specific primer low-resolution typing for HLA class I and genomic high-resolution DNA-based typing for HLA class II. Stem cell source was either bone marrow (n = 9) or peripheral blood stem cells (n = 92) from HLA-matched related donors (n = 37), HLA-matched unrelated donors (n = 52), or HLA-mismatched donors (n = 12) (Table 1). Leukocyte engraftment was defined as the first of 3 consecutive days with a leukocyte count >1000 μL and/or a neutrophil count >500 μL. Platelet engraftment was defined as the first of 3 consecutive days with a platelet count >20,000 μL without transfusions. Acute GVHD (aGVHD), late aGVHD, and chronic GVHD (cGVHD) were classified according to the National Institutes of Health consensus criteria [37], as described previously [38].

Donor Lymphocyte Infusion

Donor lymphocyte infusion (DLI) were administered to 38 patients according to a standard protocol [38,39] in a preemptive manner for patients with persistent or recurrent mixed chimerism (n = 16) or MRD (n = 2), in a prophylactic manner for patients with active disease at transplantation (n = 13), or in a therapeutic manner for morphological relapse after salvage chemotherapy (n = 7). DLI was given at 4-week intervals in escalating doses (related donor: 1 × 10^7, 5 × 10^7, and 1 × 10^8 CD3$^+$ cells/kg body weight; unrelated donor: 5 × 10^6, 1 × 10^7, 5 × 10^7, and 1 × 10^8 CD3$^+$ cells/kg body weight) after previous discontinuation of immunosuppression and only in the absence of GVHD and infection.

Chimerism and MRD Analysis

Chimerism analysis was performed at the Institute of Legal Medicine and Forensic Sciences, Charité–University Medicine Berlin, and determined by a multiplex STR assay with 9 STR systems plus the amelogenin gene with fluorescence-based detection. The analysis included CD4$^+$, CD8$^+$, and CD19$^+$ cells in peripheral blood and CD34$^+$ cells in bone marrow, at a sensitivity of 10^{-2} [40]. Chimerism analysis was performed routinely at 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months after transplantation. Patients with no signal of host DNA during follow-up were categorized as having complete donor chimerism (CC), whereas patients with a measurable host signal but not more than 5% at any time point were categorized as low-level mixed chimerism (ll-MC). Patients with a ≥5% increase in autologous cells between 2 consecutive assessments were classified as having increasing mixed chimerism (in-MC), whereas patients with a host signal immediately post-transplantation that decreased spontaneously were categorized as having decreasing mixed chimerism (de-MC) [20].

MRD analysis was performed at the GMALL study group central MRD laboratories, as described in detail elsewhere [16,35,41,42]. In brief, for BCR-ABL–positive ALL, complementary DNA was synthesized from RNA and BCR-ABL qPCR was performed, using ABL as the housekeeping gene [42]. For BCR-ABL–negative ALL, clonal Ig/TCR gene rearrangements were identified by gene scanning and/or heteroduplex gel analysis and then sequenced. MRD was then determined by clone-specific qPCR, with the aim of using 2 molecular markers with a sensitivity of at least 10^{-4}. MRD relapse was

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