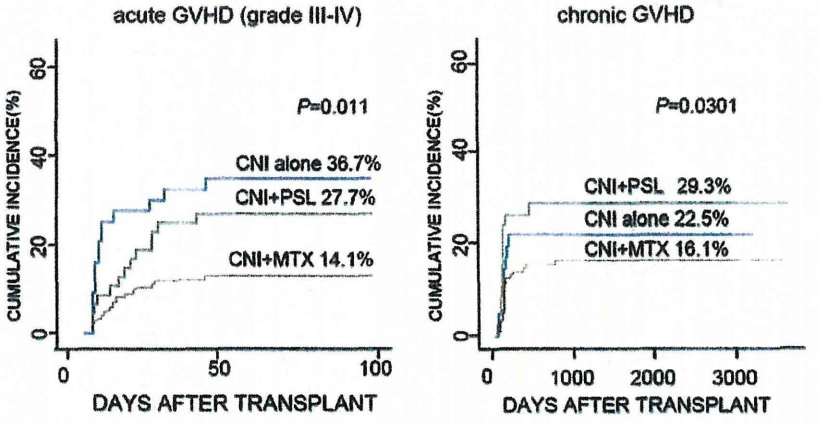

Figure 1. Cumulative incidence of aGVHD (grade III-IV) (left) and cGVHD (right). GVHD prophylaxis with CNI + MTX is associated with significantly lower incidence of aGVHD and cGVHD.

status at transplantation was significantly associated with lower EFS (Table 2).

DISCUSSION

The outcomes of CBT according to the disease status at transplantation in children with ALL were reported from a multicenter study of Eurocord. The disease-free survival (DFS) rates of those patients transplanted at complete remission and at more advanced stages were 36%-49% and 10%-18%, respectively [11-13]. In contrast to these multicenter studies, single or small numbers of institutions report better results. A study from Minnesota University reported that the EFS of children with ALL in standard and high-risk patients are 55% and 32%, respectively [14]. In the Cord Blood Transplantation (COBLT) study, the OS of children with ALL was around 60% in first and second remission [15], and a study in Denver [16] reported DFS of 62% including standard and high-risk patients. Our study is a retrospectively reviewed multicenter study with a large number of children with ALL, and the EFS or OS is comparable to that of these single-center studies.

The relevance of HLA disparity to clinical outcome in unrelated CBT has been reported by several investigators. In an International Bone Marrow Transplant Registry (IBMTR) study, the OS of serologically 6/6-matched CBT was significantly better than that of mismatched CBT, irrespective of the cell dose of the CB unit [17]. In Eurocord, the serologic disparity of HLA was reported to be important for engraftment and relapse but not for GVHD or survival, namely, serologic HLA mismatch reduced the relapse rate after transplantation. In those studies, HLA disparity in high resolution did not affect any clinical outcomes [18]. In our study, HLA disparity in low resolution affected the neutrophil engraftment and GVHD or cGVHD but not for relapse and survival. The OS according to the HLA disparity in high resolution gradually declined as the HLA disparity increased, even though this was not statistically significant in univariate analysis.

The different results regarding risk factors for relapse between our data and Eurocord may be explained by the difference of the patient population. Our study

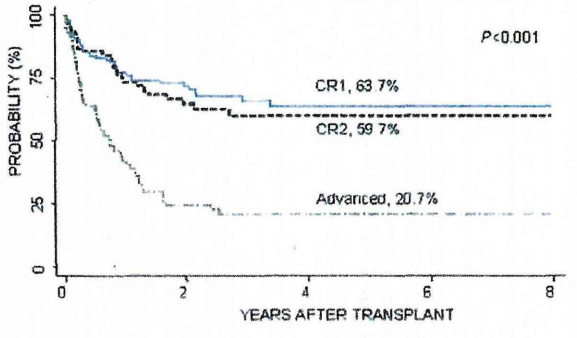

Figure 2. Probability of overall survival of patients according to disease status at transplantation. Patients with CR1 and CR2 are associated with significantly better overall survival compared with patients with advanced stage.

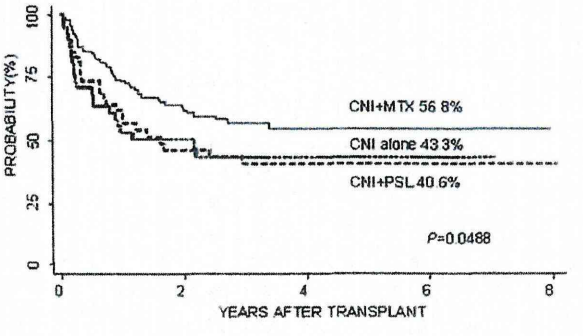

Figure 3. Probability of overall survival of patients according to GVHD prophylaxis. Patients with GVHD prophylaxis of CNI + MTX is associated with significantly better overall survival compared with patients with CNI alone or CNI + PSL.

was restricted to childhood ALL, whereas Eurocord included acute myelogenous leukemia (AML) patients [12,18], for whom a graft-versus-leukemia (GVL) effect could be more efficient than ALL patients after allogeneic SCT. Although the implications of the HLA disparity in high resolution for clinical outcome are still controversial, future study with a large number of patients could clarify the relevance of HLA disparity in high resolution on clinical outcomes.

GVHD prophylaxis after CBT is still controversial, and various methods of prophylaxis are applied in each institution or study group. In the early era of unrelated CBT, cyclosporine (CsA) and steroids with or without MTX were given as GVHD prophylaxis [19]. Subsequently, MTX was abandoned, and immunosuppression with CsA and steroids became popular in the United States and European countries. In their reports, the incidence of GVHD after CBT is 35% to 44% for grade II-IV aGVHD, 11% to 27% for grade III-IV aGVHD, and 9% to 33% for cGVHD [14,20-22], mostly by prophylaxis with CsA and steroids. GVHD prophylaxis with CNI alone after CBT was reportedly complicated with preengraftment immune reaction [23], but a Japanese retrospective study showed the superiority of GVHD prophylaxis with 2 agents compared with that of single agent in terms of DFS for patients with acute leukemia [24]. In this study, we found that the use of MTX showed favorable effects of significantly lower incidents of aGVHD and cGVHD, and in advanced cases, better OS was observed without affecting the engraftment or relapse. In Eurocord, an unfavorable effect of delayed myeloid engraftment by MTX was reported only in related CBT but not in unrelated CBT [25,26]. Another disadvantage of MTX reported by Eurocord was a higher relapse rate in unrelated CBT for children with ALL [12]. This unfavorable effect was not observed in our study, and this discrepancy could be explained by the different proportion of patients who were given ATG before SCT. In one Eurocord study for children with ALL, 88% of patients were given ATG [13], but only 7 of 270 patients (2.6%) were given ATG in our study. Because ATG reduces the incidence of aGVHD and cGVHD by purging T cells in vivo [27], GVHD prophylaxis including MTX with or without ATG needs to be analyzed in terms of transplantation outcomes including the GVL effect.

In Japan, Narimatsu [28] and Terakura [29] reported that MTX after CBT reduced the complications such as preengraftment immune reaction, engraftment syndrome, and aGVHD, as well as the incidence of treatment-related mortality and improved survival in adults. Takahashi also reported superior DFS after CBT with GVHD prophylaxis of MTX and CsA [30]. Neither of these studies found any unfavorable effects caused by MTX in unrelated CBT. In a Japanese pediatric study of CBT for AML, MTX contributed to lower TRM [31]. The critical role of MTX in unrelated CBT should be emphasized as a key drug in terms of prophylaxis for GVHD, although transplantation outcomes according to the dose and frequency of MTX administration was unable to be analyzed in this study. In our study, nobody was given mycophenolate mofetil (MMF), and the combination of CNI + MMF needs to be compared with CNI + MTX in the pediatric population.

In conclusion, CBT from an unrelated donor is feasible and effective as a treatment modality for children with ALL, and GVHD prophylaxis, which includes MTX, is critical to reduce the incidence of aGVHD and cGVHD without affecting engraftment, as well as to achieve better OS in advanced cases.

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LETTER TO THE EDITOR

Risks and benefits of ovarian shielding in female patients undergoing TBI: a decision analysis

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In a recent issue of *Bone Marrow Transplantation*, Courbiere *et al.*[1] raised the possibility of leukemia relapse after autologous transplantation of cryopreserved ovarian tissue from leukemic cell contamination in the graft. They detected a small copy number of Bcr–Abl transcripts by RQ-PCR in the ovarian tissue from an 18-year-old woman with CML. We agree that ovarian transplantation could be proposed (once patients are informed of the risk of leukemia relapse), as there were few contaminating leukemic cells and a GVL effect may be protective.

In Japan, cryopreservation of ovarian tissue is not available, but two other strategies are used to preserve fertility in young women undergoing hematopoietic SCT. One is embryo or oocyte cryopreservation for women with or without a partner, respectively. Although the success rate after transfer of thawed fertilized oocytes had been low previously, both post-thaw survival and fertilization rates of frozen oocytes[2,3] have improved. Nonetheless, concern remains regarding the potential for chromosomal aneuploidy or other karyotypic abnormalities in the offspring, as cryopreservation may affect the meiotic spindle of oocytes.[4] In addition, it is generally difficult to obtain good-quality oocytes from patients receiving chemotherapy.[5]

Another strategy is ovarian shielding in women undergoing TBI. Whereas ovarian recovery is observed in only 10–15% of patients receiving standard conditioning with CY and TBI,[6] most patients show ovarian recovery after high-dose CY alone.[6] Ovarian function can therefore be preserved by reducing the radiation dose to the ovaries. We previously reported that ovarian function was recovered in about 80% of patients who underwent ovarian shielding.[7,8] The incidence of leukemia relapse may not increase if this procedure is performed in patients in remission, as the total radiation dose to the ovaries was approximately 3 Gy in this protocol, which is higher than the TBI dose (2 Gy) in the non-myeloablative regimen of the Seattle group associated with a relapse rate similar to that of a myeloablative regimen.[9] However, a large number of patients is required to determine the actual change in the incidence of relapse under ovarian shielding.

To overcome the difficulty for both physicians and patients in deciding whether or not to perform ovarian shielding, we have used a decision analysis approach. We constructed a decision tree using TreeAge Pro 2009 software (Williamstown, MA, USA) (Figure 1). The square at the left represents a decision node. We can decide either to perform ovarian shielding or not. Circles represent chance nodes and each chance node has 2 or 3 possible outcomes with a specific probability, called the transition probability. Every branch finally ends with triangles, called terminal nodes, and each terminal node has an assigned payoff value, called utility, according to different health states. Calculations were performed backward, from right to left in the decision tree. The sum of the products of transition probabilities and the utilities of the branches becomes the expected value for each chance node, and eventually the sum of the expected values in all of the chance nodes following the decision nodes becomes the expected value of each decision. To make a simple decision model, we determined the transition probabilities based on data from patients who underwent allogeneic transplantation for acute leukemia in first remission. The incidences of transplant-related mortality and relapse were assumed to be 0.2 (20%).[10] However, the incidence of relapse may increase with ovarian shielding ('relapse after ovarian shielding' in Figure 1). Therefore, while the cure rate is '1–0.2–0.2 = 0.6 (60%)' after a decision to not perform ovarian shielding, it is '1–0.2—relapse after ovarian shielding' after a decision to perform ovarian shielding. The probability of ovarian recovery was determined to be 10% after a decision to not perform ovarian shielding and 80% after a decision to perform ovarian shielding based on the literature.[6,7] Each patient's view of life can be reflected in the value of 'alive without ovarian recovery'. Under the simple assumption that the payoff values of transplant-related mortality and relapse were both 0 points and the payoff value of cure with ovarian recovery is 100 points, each patient can score the payoff value for 'alive without ovarian recovery' based on her own view of life. Patients for whom ovarian recovery is very important assign a low payoff value for 'alive without ovarian recovery'.

The expected values for the decisions vary according to the values of 'relapse after ovarian shielding' and 'alive without ovarian recovery'. For example, if we fix the value of 'relapse after ovarian shielding' at 30% under the assumption that the incidence of relapse is increased by 10% under ovarian shielding, the expected values for the two decisions vary according to the value of 'alive without ovarian recovery', as shown in Figure 2a (one-way sensitivity analysis). The expected value for a decision to not perform ovarian shielding is higher than that to perform ovarian shielding when a patient scores 'alive without ovarian recovery' higher than 77.3 points. If we fix the value of 'relapse after ovarian shielding' at 40%, the expected value for a decision to not perform ovarian

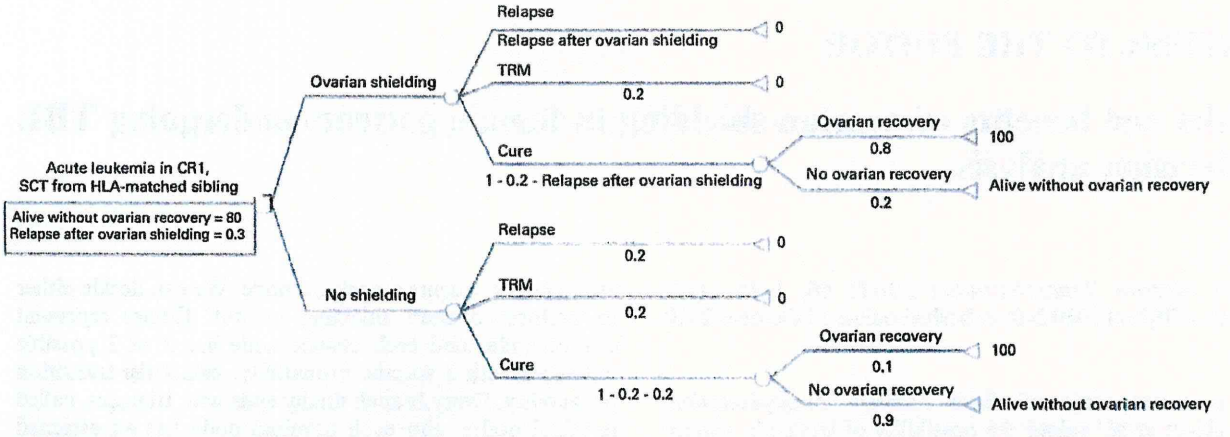

Figure 1 The decision tree used in this decision analysis.

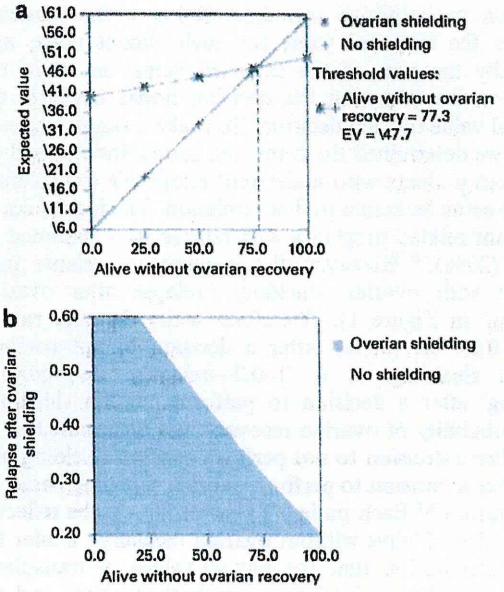

Figure 2 One-way (**a**) and two-way (**b**) sensitivity analyses. In the gray area, the expected value of a decision to perform ovarian shielding is higher than that of a decision to not perform ovarian shielding.

shielding is higher than that to perform ovarian shielding when a patient scores 'alive without ovarian recovery' higher than 56.5 points.

These two values can be changed simultaneously, as shown in Figure 2b (two-way sensitivity analysis). The threshold of the relapse rate, at which there is a change in which decision is made, can be obtained by drawing a vertical line from the 'alive without ovarian recovery' value for each patient. For example, if a patient scores 50 points for the payoff value of 'alive without ovarian recovery', the expected value for a decision to not perform ovarian shielding is higher than that to perform ovarian shielding when 'relapse after ovarian shielding' is higher than 43%, as the vertical line from the X-axis at 'alive without ovarian recovery' of 50 points crosses the borderline of the gray and white areas at 'relapse after ovarian shielding' of 43%.

Although this decision analysis is not definitive, it may be helpful for patients who find it difficult to make a decision when faced with uncertainty. Some young female patients tend to overestimate the value of fertility in their subsequent life, and we should inform patients that they can become pregnant using a donated oocyte even after their ovarian function is lost.

Conflict of interest

The authors declare no conflict of interest.

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Minimal Residual Disease following Allogeneic Hematopoietic Stem Cell Transplantation

Nicolaus Kröger,[1] Koichi Miyamura,[2] Michael R. Bishop[3]

Minimal residual disease (MRD), both before and after transplantation, is a clinically important yet relatively poorly defined aspect of allogeneic hematopoietic stem cell transplantation (alloHSCT). The clinical relevance of MRD in the context of alloHSCT has been demonstrated by its association with the development of clinical relapse. However, with the possible exception of chronic myeloid leukemia (CML), the specific techniques, timing, frequency, and clinical utility, relative to improvement in patient outcomes, for monitoring MRD in the setting of alloHSCT has yet to be clearly defined. A concise overview of monitoring techniques for detecting MRD, as well as treatment strategies and biological and clinical research initiatives for MRD suggested by the National Cancer Institute First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation, is covered in this article.

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KEY WORDS: Minimal residual disease, Allogeneic, Relapse, Graft-versus-tumor, DLI

INTRODUCTION

Minimal residual disease (MRD), in the setting of allogeneic hematopoietic stem cell transplantation (alloHSCT), poses several interesting questions and complex challenges. The relevance of these questions and challenges is personified by the relationship between MRD and the risk of relapse, which is primary cause of treatment failure and death after alloHSCT [1]. The clinical relation of posttransplant MRD with relapse, particularly in relationship to chronic myeloid leukemia (CML), was recognized early with development of cytogenetic and molecular techniques of detection [2]. The clinical relevance of MRD has been further recognized with the increased use of nonmyeloablative and reduced-intensity conditioning (RIC) regimens, with which relapse is even a greater clinical problem [3,4].

Despite the clear association of MRD with relapse, the clinical relevance of MRD in the alloHSCT setting remains to be determined. First and foremost, the definition of MRD needs to be defined for each disease, and needs to be distinguished from what we currently refer to as "remission" or "relapse." The detection of persistent disease posttransplant by immunophenotypic measures has significantly different implications for patients with acute lymphocytic leukemia (ALL) compared to someone with persistent chronic lymphocytic leukemia (CLL) [5,6]. Similarly, the molecular detection of a cytogenetic abnormality in the posttransplant is markedly different for a patient transplanted with chronic myeloid leukemia (CML) compared to a patient with acute myeloid leukemia (AML) [7]. Second, when and how often we should be using available techniques for a specific disease remains to be defined. This applies not only to the posttransplant setting, but also to the pretransplant setting, where multiple studies have demonstrated the prognostic significance of MRD prior to conditioning [8]. As the majority of relapses occur within the first 6 months after transplantation [1], it is important to determine the frequency of monitoring for recurrent disease within this posttransplant period. If we can determine when and how often, the next question is what tests should we be performing and are those tests adequately sensitive, specific, reproducible, practical, and economical. Finally, and most importantly, does monitoring for MRD make a clinical difference? There is sufficient evidence that detection of MRD provides prognostic information. However, does this information result in clinical decisions, relative to choice of conditioning regimen or stem cell product relative to detection of pretransplant MRD or intervention (eg, withdrawal of immune suppression

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or donor lymphocyte infusion) that result in improved outcomes? These remain essential questions for which there are relatively limited data and recommendations, with the possible exceptions of CML and ALL, and even with these diseases, there remains a need for further investigation.

This manuscript attempts to provide a concise overview of many of these issues. Specifically, it attempts to address methods for monitoring MRD and strategies to clinically manage patients once MRD is detected. In addition, a brief summary is provided on the National Cancer Institute First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation, which attempted to address in a formal manner many of the issues described above.

MONITORING MRD AFTER ALLOSCT

Improved supportive care, the introduction of RIC regimen, and careful donor selection have substantially decreased the nonrelapse mortality (NRM) after alloHSCT in recent years, and therefore relapse has become the leading cause of death following alloHSCT. Furthermore, as inferred above, relapse remains the primary cause of death among patients surviving more than 2 years after alloHSCT [9]. Despite improved understanding of the biology that underlies the graft-versus-leukemia/tumor (GVL/GVT) effect, the relapse rate has not decreased over the past 20 years [10,11]. It is obvious that relapse after alloHSCT evolves from residual disease that escaped the preceding conditioning regimen as well as the graft-versus-malignancy effect.

New methodologic and technologic advances allow sensitive detection of MRD and early recognition of recurrence after alloHSCT. This is of clinical importance because intervention prior to florid relapse improves outcome for certain hematologic malignancies [12,13]. Standard diagnostic criteria that are widely employed in the definition of relapse for the different hematologic malignancies are based on morphologic bone marrow investigations, imaging, and/or specific laboratory findings. After alloHSCT, more sensitive methods, such as tumor-specific molecular primers, molecular genetics, fluorescence in situ hybridization (FISH), flow cytometry, and/or chimerism analysis, are commonly used to monitor patients with respect to relapse (Table 1).

Broadly, 2 different approaches are mainly used for the posttransplant surveillance of disease status: characterization of chimerism, and specific detection of MRD. The latter approach measures the malignant clone directly, whereas chimerism assessment characterizes the origin of posttransplant hematopoiesis. For chimerism as well as for specific detection of residual disease, a variety of techniques are available, although in general, there have been more studies looking directly at markers of residual tumor than of chimerism [14]. Despite the increasing sensitivity by the described methods of chimerism determination, because of its low specificity, this method is not a reliable means of detecting MRD. The specificity is higher in diseases that originate from a stem or progenitor cell (eg, AML, CML), whereas in B cell lymphoma or multiple myeloma, which originate from a late B cell stage of development, the specificity of chimerism to detect MRD or relapse is low. The lack of specificity might be overcome partly by performing lineage-specific chimerism in some diseases such as multiple myeloma [15].

A paradigm for the importance of minimal molecular disease and prediction of relapse after alloHSCT is CML. Here, it is now well established that the detection of the chimeric *BCR-ABL* mRNA transcript by reverse-transcriptase polymerase chain reaction (RT-PCR) is a powerful predictor of subsequent relapse [16]. The use of quantitative PCR has greatly increased the clinical value of monitoring MRD. It could be demonstrated that the kinetics of BCR-ABL level over time described impending relapse and response to donor lymphocyte infusion (DLI). Low or absence of residual BCR-ABL was associated with a very low risk of relapse (1%), compared to 75% relapse rate in CML patients with increasing or persistently high BCR-ABL levels [17]. The activating mutation V617F of the *JAK2* gene is an obvious target for monitoring MRD in patients with myeloproliferative disorders undergoing alloHSCT. There are emerging data suggesting that, similar to *BCR-ABL* in CML, PCR negativity for *JAK2-V617F* correlates with prolonged remission and that reappearance of a detectable *JAK2-V617F* clone is associated with relapse [18].

However, the utility of the available tools in the monitoring of disease status after alloHSCT has not yet been fully elucidated across all hematologic malignancies. In AML and myelodysplastic syndromes, several studies demonstrated the relevance of chimerism, and especially its kinetics, for the prediction of relapse. A variety of genetic markers are available for MRD in AML such as rearrangements t (15;17)/*PML-RARA*, inv(16)/*CBFB-MYH11*, and t(8;21)/*RUNX1-RUNX1T1*, *NPM1*, *FLT3*, or *MLL-PTD* but have not been studied in a larger cohort of patients.

Methods for MRD monitoring in B- or T-lymphoid malignancies include PCR techniques aiming to quantitatively detect disease specific T cell receptor (TCR) or immunoglobulin (Ig) gene rearrangements. Multiple studies support the independent prognostic value of MRD measurements in pediatric and adult patients with B- and T-lineage ALL. Furthermore, the risk of relapse appears to be proportional to the level of MRD, which in some studies was found to be the most powerful prognostic factor for relapse in

Table 1. Diagnostic Methods to Monitor Residual Disease and Relapse after Allogeneic Stem Cell Transplantation

Detection of Residual Disease (MRD)	Karyotyping	FISH	Flow Cytometry	Antigen Receptor PCR	Translocation or Other mRNA PCR	Chimerisms: XY FISH	Chimerism: qPCR/VNTR-PCR
Utility	Subset of all types of neoplasms with chromosomal abnormalities	Subset of all types of neoplasms with know chromosomal abnormality	ALL; most AML; CLL; myeloma	ALL; lymphoma, myeloma	CML; subset of ALL; subset of AML; subset of lymphoma	All types of neoplasms (sex mismatched SCT) Disadvantage not specific for MRD	All neoplasms (precondition differences in donor/recipient polymorphisms) Disadvantage: not specific for MRD
Sensitivity	10^{-1}	10^{-2}	10^{-3}-10^{-4}	10^{-4}-10^{-5}	10^{-3}-10^{-6}	10^{-2}	10^{-3}-10^{-6}

qPCR indicates quantitative real-time PCR (modified after [6]); CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; VNTR, variable number tandem repeat.

multivariate analyses [13]. Similarly, detection of pretransplant MRD in pediatric and some adult studies is highly predictive of relapse following alloHSCT and, coupled with posttransplant MRD evaluation, may guide early posttransplant intervention such as early withdrawal of immunosuppression, administration of DLI, or addition of posttransplant maintenance therapy (eg, targeted tyrosine kinase inhibition for Ph+ ALL).

In CLL, 2 main approaches of MRD assessment have been followed: flow cytometry, taking advantage of the unique immunophenotype of CLL, and PCR-based strategies using the clonal rearrangement of the hypervariable region of the V_H part of the immunoglobulin heavy chain gene (CDR3 region). Several studies showed that MRD assessment after alloHSCT is predictive for durable freedom from CLL progression if: (1) MRD levels are below 1×10^{-4} at 1 year posttransplant, or (2) show decreasing or stable kinetics within the quantitative range. The clinical impact of MRD detection in different lymphomas is not identical.

Specific chromosomal translocations detectable by PCR amplification, particularly t(11;14) and t(14;18) translocation, are present in mantle cell lymphoma and follicular lymphoma, respectively, but t(14;18) translocation is also detectable by PCR at low levels in 10% to 25% of healthy individuals. For Hodgkin lymphoma, neither cytogenetics, flow cytometry, nor molecular testing is helpful for assessing residual disease [19].

In multiple myeloma, MRD can be detected by PCR using patient-specific primers derived from the rearrangement of immunoglobulin heavy-chain genes. It could be shown that durable PCR-negativity after allografting had a cumulative risk of relapse at 5 years of 0%, in comparison to 33% for PCR-mixed patients and 100% for patients who never achieved PCR-negativity [20]

Ongoing and further clinical trials investigate whether sensitive MRD detection will allow for earlier therapeutic intervention, and it is hoped that treatment prior to overt relapse may improve outcome of allogeneic stem cell transplantation for hematologic malignancies.

STRATEGIES AND OPTIONS FOR RECURRENT DISEASE FOLLOWING ALLOSCT

The clinical significance of MRD after alloHSCT is different among diseases. MRD has been extensively studied using the qualitative PCR method during the early 1990s. Detection of BCR-ABL by PCR in the first year after alloHSCT for CML patients disappears in the majority of patients, secondary to ongoing GVT

effects; however, detection of MRD after alloHSCT for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) is indicative of imminent hematologic relapse [21-24]. In the case with t(8;21) AML, MRD after chemotherapy does not always indicate eventual clinical relapse. In the last decade, quantitative PCR machines are widely available, and sequential and quantitative tests of leukemic genes have become available. With this technique, a rise in the amount of leukemic genes strongly suggests clinical relapse in the near future. Also, several investigators have tried to find thresholds for the amount of genes that are predictive of clinical relapse. However, because of a lack of standardization of this technique, hitherto universal threshold has not been clarified at any leukemia with the possible exception of CML.

Clinical Intervention

Because of the limitation of quantitative PCR as mentioned above, clinical intervention upon the emergence of MRD has not been well established. Clinical interventions for early relapse and MRD after alloHSCT are performed in 2 ways; 1 is adoptive immunotherapy including DLI and vaccination, and the other is administration of new agents, which are expected to preserve normal hematopoietic cells. Several questions are raised in this clinical setting. First, does early intervention have more clinical effects than the intervention performed at hematological relapse? Second, does clinical intervention affect the other parameters such as graft-versus-host disease (GVHD), related adverse events, and the subsequent alloHSCT. Third, which is the better way, prophylactic administration or intervention upon MRD, for patients with a high risk of relapse?

Adoptive Immunotherapy

DLI was first developed for relapsed patients. Although they are dramatically effective for CML, DLI remains limited of limited utility for patients with other diseases because of inadequate responses and toxicity related to GVHD, which occurs in one-third of patients. As a strategy to reduce the incidence and severity of GVHD while preserving the GVL effect, tumor-specific DLI are proposed [25]. A protocol to generate hematopoietic cell–specific minor antigen (eg, HA-1, HA-2, ACC-1) specific T cell lines from mHag-negative donors was studied for adoptive immunotherapy. Warren et al. [26] conducted a phase I/II study to test the toxicity and effectiveness of CTL clones specific for minor H antigens. However, this strategy using cloned antigen-specific T cells has been shown to be ineffective mostly because these cells could not survive long enough to execute their cytotoxic ability in vivo. This problem could be overcome by: (1) infusion of a relatively young and small number of memory T cells without extensive expansion in vitro, and (2) infusion of autologous peripheral blood T cells transduced retrovirally with T cell receptor α and β cDNA cloned from tumor/minor antigen–specific T cell clones [27]. The latter approach has been shown to be promising in the setting of melanoma treatment in studies conducted by Rosenberg and colleagues at the National Cancer Institute [28]. Thus, T cells armed with TCR specific for WT-1, HA-1, HA-2, and ACC-1 would be great candidates for adoptive immunotherapy in the very near future. Another approach studied intensively in the clinical hematology field is a vaccination using epitope peptides such as WT-1, PR3, MUC-1, NY-ESO-1, and BCR-ABL fusion polypeptides. In particular, WT-1 is one of the most promising tumor antigens because WT1 vaccination-driven immunologic responses and clinical responses, including reduction of leukemic cells, and the reduction of the M-protein amount in myeloma, have been reported. Further enhancement of the efficacy of the WT1 peptide vaccine can be expected by coadministration of WT1-specific helper peptide, Th1-inducing adjuvant, or immunosuppressive chemotherapy prior to vaccinations to take advantage of inhibition of regulatory T cells and facilitation of homeostatic expansion of desired T cells. Adoptive immune therapies as prophylaxis or preemptive therapy would be performed in the near future.

New Agents

Chemotherapy for the patients with recurrent disease is hampered by the fact that these agents impel the normal hematopoietic cells, as well as the fact that tumor cells and tumor-specific agents have long been desired. Recently, a new molecular-specific targeting agent has been developed. The specific manner of these new agents prompts us to use them for earlier interventions. Nevertheless, most of these tumor-specific agents exert some effects on normal hematopoietic cells and interfere with immunologic functions after alloHSCT.

Tyrosine kinase inhibitors

Philadelphia chromosome-positive ALL is associated with highly aggressive disease. Although alloHSCT is at present the only curative treatment option, hematologic relapse still remains a major obstacle. Recently, there have been some reports of posttransplant imatinib administration, but its efficacy and administration methods are still controversial. Nishiwaki and colleagues [29] compared prophylactic administration of imatinib with intervention upon molecular relapse to evaluate the effect of posttransplant imatinib administration. MRD became positive in both groups, leading to hematologic relapse. It was therefore concluded that