However, these reports preceded the definition of NK cells and our understanding of the molecular basis of PNH, prompting reassessment. Mosaicism in PNH\(^1\) allows side-by-side functional comparisons of GPI\(^+\) and GPI\(^{-}\)NK cells within individual patients, enabling the assessment of NK cell activity on a per cell basis (Figure 1; supplemental Figure 1, available on the Blood Web site). Despite reports of impaired activity,\(^3,4\) the GPI-deficient NK cells were proficient at target cell-induced granule exocytosis (Figure 1A-B; supplemental Figure 1). Thus, early findings associating reduced NK cell activity with reduced LGL numbers rather than intrinsic cellular activity are correct.\(^4\) The absolute number of NK cells (and more variably, other lymphocytes) is indeed reduced in PNH\(^7\); in our cohort of 39 patients, two thirds had NK cell counts below the reference range (Figure 1C), and NK cell numbers were not significantly correlated with neutrophil, monocyte, or platelet counts (supplemental Figure 2). The basis for reduced NK cell numbers in PNH is unclear, although this might be related to impaired chemotactic or homeostatic mechanisms, as we recently reported.\(^5\) Although the activity of GPI-deficient NK cells is unimpaired, a reduction in absolute numbers of NK cells will reduce NK cell activity in the blood as a whole.

Clearly, PNH should not be classified as a functional NK cell deficiency (NKD). Classical NKD is characterized by \(\approx 1/10\) the normal number of NK cells, and counts in most of our PNH patients exceeded this (Figure 1C). Furthermore, the term NKD is reserved for where “the impact upon NK cells need represent the major immunological abnormality in the patient.”\(^6\) In PNH, all hematopoietic lineages are affected because of the presence of PIGA mutations in hematopoietic stem cells.\(^1\) More compelling is the clinical phenotype; the defining feature of NKD is the heightened susceptibility to viruses,\(^5,6\) which has not been observed in PNH.\(^7,9,10\) Instead, infection in PNH is bacterial in origin\(^10\) and likely to be associated with neutropenia secondary to underlying bone marrow failure or associated with use of eculizumab, which increases the risk of infection with encapsulated bacteria normally eliminated by terminal complement components.\(^1\) In summary, the low numbers of NK cells in PNH affect overall cytotoxicity, but this defect is not severe enough to manifest as heightened susceptibility to viral infection as seen in NKD.

Yasser M. El-Sherbiny
Leeds Institute of Cancer and Pathology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds School of Medicine, Leeds, United Kingdom
Clinical Pathology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Gina M. Doody
Leeds Institute of Cancer and Pathology, University of Leeds School of Medicine, Leeds, United Kingdom

Richard J. Kelly
Leeds Institute of Cancer and Pathology, University of Leeds School of Medicine, Leeds, United Kingdom

Anita Hill
Leeds Institute of Cancer and Pathology, University of Leeds School of Medicine, Leeds, United Kingdom

Peter Hillmen
Leeds Institute of Cancer and Pathology, University of Leeds School of Medicine, Leeds, United Kingdom

Graham P. Cook
Leeds Institute of Cancer and Pathology, University of Leeds School of Medicine, Leeds, United Kingdom

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Correspondence: Graham P. Cook, Leeds Institute of Cancer and Pathology, University of Leeds, Wellcome Brenner Building, St James’s University Hospital, Leeds LS9 7TF, United Kingdom; e-mail: g.p.cook@leeds.ac.uk.

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To the editor:

Comparison of transplantation with reduced and myeloablative conditioning for children with acute lymphoblastic leukemia

Allogeneic stem cell transplantation (SCT) for patients with acute lymphoblastic leukemia (ALL) is mostly undergone with myeloablative conditioning (MAC) and it could be the major cause of short- or long-term complications such as endocrinologic disorders including hypogonadism or growth hormone-deficient short stature.\(^1,2\) In recent years, SCT with reduced-intensity conditioning (RIC)
regimens was introduced for children who have pretransplant morbidity or are unable to tolerate a MAC regimen. Although it has the possibility of reducing posttransplant late toxicities, the exact clinical implications of a RIC regimen are still unclear. Therefore, in this study, we retrospectively compared the transplant outcomes with RIC and MAC regimens for children with ALL to determine the feasibility of SCT with a RIC regimen using the Transplant Registry Unified Management Program (TRUMP), a nationwide database established by the Japan Society for Hematopoietic Cell Transplantation (JSHCT).

We analyzed 1334 children with ALL who underwent allogeneic SCT as the first transplant from January 2000 to December 2010 in Japan; they consisted of 1201 patients with a MAC regimen and 133 patients with a RIC regimen according to the intensity of the conditioning regimen. The definition of RIC or MAC was based on the internationally recognized criteria, in which MAC is defined as fractionated total body irradiation (TBI) of $\geq 8$ Gy, single TBI of $\geq 5$ Gy, or busulfan of $\geq 8$ mg/kg or $\geq 280$ mg/m$^2$, and other regimens are categorized as RIC. Patients were transplanted at first complete remission (CR1, n = 568), second complete remission (CR2, n = 374), or advanced stages (third or further remission and relapse, n = 371), and there was no significant difference between RIC and MAC in this regard ($P = .125$). The type of SCT according to the stem cell source was related bone marrow transplantation (n = 413), related peripheral blood stem cell transplantation (n = 89), unrelated bone marrow transplantation (n = 446), or unrelated cord blood transplantation (n = 386); the serological HLA disparity between donor and patient was none (n = 816) or mismatched (n = 486) for the graft-versus-host direction, and the number of mismatched transplants was significantly higher in RIC patients ($P = .007$).

At a median follow-up of 765 days, 5-year overall survival (OS) rates of patients with RIC and MAC were 52.4% and 56.1% ($P = .525$) and they were 75.2% and 73.4% at CR1 ($P = .991$), 50.5% and 56.7% at CR2 ($P = .747$), and 26.7% and 30.3% at more advanced stages ($P = .683$), respectively (Figure 1A). Five-year relapse-free survival rates were 43.0% and 52.4% in RIC and MAC ($P = .070$) and were 62.3% and 68.2% at CR1 ($P = .249$), 46.6% and 54.0% at CR2 ($P = .520$), and 14.9% and 27.0% at more advanced stages ($P = .295$), respectively. Relapse was observed in 434 patients (54 with RIC and 380 with MAC), which included 125 in CR1, 110 in CR2, and 194 in advanced stages at SCT. The cumulative incidence of relapse rates at 5 years were 43.1% in RIC and 33.6% in MAC ($P = .020$). The 5-year relapse rates of RIC and MAC at each disease status of SCT were 30.9% and 23.3% at CR1 ($P = .129$), 36.7% and 30.4% at CR2 ($P = .548$), and 52.8% at more advanced stages ($P = .211$), respectively (Figure 1B). Treatment-related mortality (TRM) among all patients was observed in 196 patients (18 with RIC and 178 with MAC) and the cumulative incidences of TRM at 5 years were 43.1% in RIC and 33.6% in MAC ($P = .020$). The 5-year relapse rates of RIC and MAC at each disease status of SCT were 30.9% and 23.3% at CR1 ($P = .129$), 36.7% and 30.4% at CR2 ($P = .548$), and 63.5% and 52.8% at more advanced stages ($P = .211$), respectively (Figure 1B). Treatment-related mortality (TRM) among all patients was observed in 196 patients (18 with RIC and 178 with MAC) and the cumulative incidences of TRM at 5 years were 43.1% in RIC and 33.6% in MAC ($P = .020$). The 5-year relapse rates of RIC and MAC at each disease status of SCT were 30.9% and 23.3% at CR1 ($P = .129$), 36.7% and 30.4% at CR2 ($P = .548$), and 63.5% and 52.8% at more advanced stages ($P = .211$), respectively (Figure 1B). Treatment-related mortality (TRM) among all patients was observed in 196 patients (18 with RIC and 178 with MAC) and the cumulative incidences of TRM at 5 years were 43.1% in RIC and 33.6% in MAC ($P = .020$). The 5-year relapse rates of RIC and MAC at each disease status of SCT were 30.9% and 23.3% at CR1 ($P = .129$), 36.7% and 30.4% at CR2 ($P = .548$), and 63.5% and 52.8% at more advanced stages ($P = .211$), respectively (Figure 1B).

**Figure 1. Probability of OS and cumulative incidence of relapse of children who underwent transplantation at CR1, CR2, and advanced stages with RIC and MAC regimen. (A) Probability of OS. (B) Cumulative incidence of relapse.**
TRM (HR = 0.89, 95% CI = 0.55-1.44, P = .621), and neutrophil engraftment (HR = 0.99, 95% CI = 0.79-1.26, P = .983).

In conclusion, the transplant outcomes of children with ALL who were given an RIC regimen in allogeneic SCT were not significantly different from those with a MAC regimen. Because this is a registry-based retrospective study and the number of patients with an RIC regimen is small, the results should be interpreted with caution. We need to proceed to a prospective study to prove the feasibility of SCT with an RIC regimen in children with ALL in order to reduce the transplant-related toxicities, especially in terms of the late effects after SCT.

Koji Kato
Department of Hematology and Oncology, Children’s Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

Motohiro Kato
Department of Pediatrics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Daichiro Hasegawa
Department of Hematology and Oncology, Kobe Children’s Hospital, Kobe, Japan

Hirohide Kawasaki
Department of Pediatrics, Kansai Medical University Hirakata Hospital, Osaka, Japan

Hiroyuki Ishida
Department of Pediatrics and Blood and Marrow Transplantation, Matsushita Memorial Hospital, Moriguchi, Japan

Yasuhiro Okamoto
Department of Pediatrics, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

Katsuyoshi Koh
Department of Hematology/Oncology, Saitama Children’s Medical Center, Saitama, Japan

Masami Inoue
Department of Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan

Jiro Inagaki
Department of Pediatrics, National Kyushu Cancer Center, Fukuoka, Japan

Keisuke Kato
Division of Pediatric Hematology and Oncology, Ibaraki Children’s Hospital, Mito, Japan

Hisashi Sakamaki
Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Koike Kato designed the study; Koji Kato, M.K., and Y.A. analyzed and interpreted the data; M.K., D.H., H.K., H.I., Y.O., K. Koh, M.I., J.I., Keisuke Kato, and H.S. collected and assembled the data; Koji Kato, H.S., H.Y., and K. Kawa controlled patient registration; Koji Kato, M.K., R.S., and Y.A. critically reviewed the data; and all authors provided final approval of the manuscript.

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Correspondence: Koji Kato, Department of Hematology and Oncology, Children’s Medical Center, Japanese Red Cross Nagoya First Hospital, 3-35, Michishita-cho, Nakamura-ku, Nagoya 453-8511, Japan; e-mail: kokato@nagoya-1st.jrc.or.jp.

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