The Current State of Transfusion Medicine and Cell Therapy

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Shigeyoshi MAKINO,[*1,2] Shuichi KINO,[*2] Nelson Hirokazu TSUNO,[*2] Koki TAKAHASHI[*2]

Transfusion medicine in Japan is supported by the blood donation system. After the cabinet's decision to unify the blood donation system to the Japanese Red Cross Blood Center (JRCBC) in 1964 triggered by the tragic incidence involving the Ambassador from the U.S., Mr. Edwin Oldfather Reischauer, a blood center was established in every prefecture in Japan, and since 1969, all blood products for transfusion have originated from blood donation. Afterward, the blood component transfusion became the standard procedure; the blood collection criteria were revised. In 1986, the 400-mL blood donation and component donation were introduced, which constitute the basis of the present donation system. Since 1985, the use of plasma derivatives, especially albumin, has been extremely high, approximately 1/3 of the total produced worldwide being consumed in Japan, which depended on up to 95% importation. In reaction to a corrective action request by the WHO, the Japanese government released guidelines and criteria for implementing the appropriate use of blood products, which were subsequently revised, and the presently defined "Guidelines of Transfusion Practice" and the "Criteria for the Use of Blood Products" were announced. With the implementation of these measures, the use of albumin has significantly decreased, and the domestic self-sufficiency rate has achieved levels surpassing 50%, but recently, as a result of the gap in price between national and international products, the trend has temporarily leveled off.

The safety of blood products has remarkably improved with the introduction of screening tests for donated blood. In addition to detection of the serological markers of hepatitis and human immunodeficiency virus, the nucleic acid amplification test for viral markers was introduced in 1999, and furthermore, the provision of irradiated blood to prevent the harmful graft-versus host disease was started in 1998. Also, since 2004, the pre-storage leukocyte reduction of all blood products was introduced to prevent non-hemolytic transfusion reactions, and since 2006, diversion of the initial blood flow during blood collection was implemented to prevent bacterial contamination of blood products. Additionally, for the prevention of transfusion-related acute lung injury, more than 99% of the 400 mL-derived fresh-frozen plasma is derived from male blood donors, avoiding to the extent possible the transfusion of plasma from multiparous women, which may contain the causative anti-leukocyte antibodies.

Following the Product Liability Act of 1995, in 2003, the Law for the Stable Provision of Safe Blood Products was enacted, which established 1) the improvement of the safety of blood products, 2) the domestic self-sufficiency through blood donation, as a general rule, and the guarantee of stable provision, 3) the promotion of appropriate use, 4) the clarification of the roles of medical and paramedical staff dealing with blood transfusions, based on the fundamental principles for guaranteeing fair and transparent blood business operations. In 2004, "the relief system for the victims of virus transmission through biological products" was established, and in 2005, the "guideline for the look back study of blood products" was implemented. In addition, the blood transfusion management

*1 Department of Transfusion Medicine, Toranomon Hospital, Tokyo, Japan (s-makino@toranomon.gr.jp).
*2 The Japan Society of Transfusion Medicine and Cell Therapy, Tokyo, Japan.

system was consolidated, consisting of nomination of a physician responsible for blood transfusion, assignment of a medical technologist responsible for blood transfusion, unified management of the transfusion service, establishment of a hospital transfusion committee, and a 24-hours-a-day provision of blood transfusion tests in each institution. Since 2006, institutions that fulfill these requirements and perform safe and appropriate transfusion practices have been paid a "transfusion management fee." The Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) adopts a team approach to perform safe blood transfusion, and for this purpose, promotes certification systems, including, in addition to the certified physician, the certified medical technologist in transfusion medicine, the JSTMCT-certified transfusion nurse, including autologous blood transfusion nurse, apheresis nurse, and clinical transfusion nurse. However, in small institutions, the establishment of an appropriate transfusion management system is difficult, thus joint transfusion committees were established in each prefecture, which are working not only for the promotion of appropriate use and reduction of blood wastage, but also for standardization of transfusion practices. In 2012, the requirements for the "transfusion management fee" were revised, and divided into facility requirements and appropriate use requirements.

According to the annual survey conducted by the JSTMCT, the number of institutions receiving blood supply from the JRCBC has surpassed 11,000, among which, 90% are small institutions with fewer than 300 beds. The total amount of blood supplied by the JRCBC progressively decreased until 2006, as a result of the promotion of appropriate use and the reduction of invasive surgical procedures. However, since 2007, consumption of all blood products has increased. One reason for this is that Japan has become a super-graying society, with an increase in the elderly population with cardiovascular diseases, who require blood transfusion. Thus, in order to guarantee a stable blood supply, additional promotion of blood donation is indispensable. As a measure to overcome this problem, the age of male blood donors was raised to 17–69 years for the 400-mL blood donation and to 18–69 years for platelet apheresis donation. Also, promotion of autologous blood transfusion is essential. Autologous blood transfusion is covered by the Japanese Universal Health Insurance, as well as the use of erythropoietin (ESA), thus, it is actively performed in Japan. Implementation of certification of nurses by the Japanese Society of Autologous Blood Transfusion, is expected to enhance promulgation of safe autologous blood transfusion, based on blood collection by expert physicians or nurses with essential knowledge on autologous blood collection, and adequate preservation of collected blood on specific refrigerators. However, the use of ESA for the treatment of chemotherapy-induced anemia (CIA) is not covered by Japanese Universal Health Insurance, and the transfusion of red blood cell concentrates remains as the only available treatment. In an attempt to guarantee the patient's freedom of treatment choice, a field survey on CIA is being conducted in conjunction with the Japan Society of Clinical Oncology, in an attempt to clarify the sample size that would benefit the use of ESA.

In 2007, the "Guideline for actions against intraoperative critical hemorrhage," which defines the prompt coordinated action of the surgeons and anesthesiologists in the field, the transfusion service and the JRCBC, in case of massive hemorrhage, was announced. However, fibrinogen preparation is not yet available for cases of dilutional coagulopathy due to massive transfusion, and a field survey is ongoing to determine the number of cases developing massive hemorrhage, in an attempt to clarify the significance of the expansion of its indication.

Cell therapy can be divided into stem cell transplantation and the other cell therapies. In Japan, more than 1,000 unrelated-donor stem cell transplantations are being performed annually. Moreover, autologous stem cell transplantation is mainly performed using frozen-preserved peripheral blood stem cells (PBSC), maintained at −80°C in CP-1 solution (a mixture of DMSO and HES) as the preservative, which is a simple preservation procedure, and is being largely applied. Since 2010, the unrelated PBSCT emerged as a new alternative, and increased use of PBSCT is expected hereafter. On the other hand, the use of cord blood stem cell mini-transplantation for the elderly is increasing rapidly, dependent on the availability of cord blood stem cells through the cord blood bank network. In 2010, the "Guideline for the manipulation of blood cells in-hospital" was announced, and adequate

manipulation of cells by the transfusion services was stimulated. Concerning the other cell therapies, bone marrow-derived cells or peripheral blood monocytes are being used for regenerative medicine targeting angiogenesis or cardiac muscle regeneration, and also LAK- or DLI-based immunotherapies are ongoing. Additionally, granulocyte transfusion for cases of severe infection during bone-marrow failure in the post-stem cell transplantation period is being performed in accordance with the "Granulocyte transfusion guideline." Hence, striking remarkable progress is expected to be made in the field of cell therapy, and the role of transfusion services, which deals with it, is also expected to be more important.