4) Treatment and Prevention of TA-GVHD (transfusion‐associated graft-versus-disease)

There is currently no effective treatment for transfusion-associated GVHD. It is therefore important to establish methods for its prevention. Irradiation of blood products containing immune cells is one way to prevent TA-GVHD. Guidelines have been created in each country and recommend the use of irradiated blood products for immunodeficient patients, as well as for premature neonates, elderly persons, immunocompromised patients including those receiving fludarabine[1)], recipients of blood from relatives that can induce TA-GVHD due to a donor-recipient combination of HLA antigens, and patients with any other conditions reported to develop TA-GVHD in literatures. With a high frequency of TA-GVHD in Japan, the Japan Society of Blood Transfusion issued the first guidelines in 1992 and made efforts to prevent TA-GVHD by conducting public relation activities for medical institutions, and revising the guidelines several times. However, in 1997, 14 of 67 suspected cases of TA-GVHD received by the hemovigilance system of the Japanese Red Cross Society (JRCS) were confirmed to be TA-GVHD, and all of 14 patients died. This fact came as a tremendous shock to the Ministry of Health, Labour and Welfare (MHLW), which issued a notification on the prevention of TA-GVHD. Probably with this notification, the number of confirmed cases of TA-GVHD decreased to 2 in 1998, but again increased to 4 in 1999. Moreover, as revealed by the Japanese Red Cross hemovigilance system, of 64 patients with confirmed TA-GVHD collected by the JRCS to that date, only one patient was immunodeficient, and the other 63 patients were immunocompetent. These data suggested that the guidelines for patient selection for the use of irradiated blood, which focus on identification of immunodeficient patients, are ineffective. It was estimated that 50-100 patients would die a year of TA-GVHD, and the MHLW directed that all cellular blood products should undergo universal irradiation before supplied by the JRC blood centers, which was started in early 2000. Fortunately, during the past 11 years from 2000 to the end of 2010, no TA-GVHD due to blood supplied by the JRCS has been reported. This means that hundreds of lives were saved, and that the doses of irradiation (minimum, 15 Gy; maximum, 50 Gy) were effective. However, another problem arose. Storage of irradiated red blood cell products increases supernatant potassium levels, and in fact, serious hazards such as cardiac arrest due to irradiated red blood cell transfusion have been reported in neonates, patients receiving massive transfusions, and patients with renal failure. For such patients, some cases successfully treated with the use of a potassium depletion filter containing potassium binding resins (Kawasumi Laboratories, Inc.) has been reported.[2), 3), 4)]

In the U.K., a new, rapidly progressive spongiform encephalopathy that was probably specific to the U.K. was reported in 1966. Although this is similar to classical CJD (Creutzfeldt-Jakob disease), it is of juvenile onset and called new variant CJD, also known as mad cow disease (MCD) in humans. The pathogen was originally of sheep origin, and transmitted to cattle by feed containing meat and bone of sheep, resulting in the MCD epidemic in cattle. It was revealed that a prion, an infectious

protein agent contained in beef could also infect humans, and transmitted from human to human through blood transfusions from people who are infected with prion but not showing symptoms yet. To combat this, leukodepletion of transfused blood has been performed all over the world. In the procedure, leukocytes, which are deemed to carry the majority of the infectious agents at a high concentration, are removed by a leukocyte depletion filter from blood immediately after collection.

Japan (in 1993), France (in 1994), and the U.K. (in 1995) established surveillance systems (hemovigilance) to collect reports of adverse reactions/events associated with blood transfusion, investigate the causes, and prevent the occurrence of adverse reactions/events. Many other countries then followed and established the same system to monitor serious adverse reactions/events associated with blood transfusion. Williamson et al.[5)] at the U.K. SHOT (Serious Hazards of Transfusion, UK hemovigilance) believed that universal leukodepletion (LD) implemented in the U.K. in 1999 could decrease the incidence of TA-GVHD because it is caused by lymphocytes, and investigated the incidence of TA-GVHD and PTP (post-transfusion purpura) reported to the SHOT between 1996 and 2005---before and after implementation of universal LD. PTP is a adverse reaction to transfused platelets and leukocyte depletion filters can also reduce platelets in red blood cell components; they therefore compared the incidence of PTP before and after universal LD. The incidence of PTP decreased from 10.3 cases year before introduction of the leukocyte depletion filter to 2.3 cases year afterward, and for TA-GVHD it decreased from 13 cases to 2 cases after implementation of LD. Considering that in addition to these two cases, there is another case, reported by Akahoshi et al. in 1992, of TA-GVHD in a patient only receiving leukodepleted blood by leukocyte depletion filters, leukodepletion of transfused blood is not completely effective in preventing TA-GVHD. Even so, the findings showed that it was an extremely effective method for its prevention; this provides important information to prevent TA-GVHD in the setting where irradiation equipment is not available.

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