Guidelines for the use of platelet transfusion concentrates based on scientific evidence

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List of Recommendations

● CQ1 How should platelet transfusion be carried out in chemotherapy for cancer/hematopoietic malignancies, autologous hematopoietic stem-cell transplantation, and allogeneic hematopoietic stem-cell transplantation?

The platelet transfusion trigger for chemotherapy for cancer/hematopoietic malignancies (except acute promyelocytic leukemia) and autologous/allogeneic hematopoietic stem-cell transplantation should be $1\times10^4/\mu L$ (2C). However, it should be modified flexibly depending on the patient's condition and medical care environment.

Platelet transfusion should be performed prophylactically in chemotherapy for cancer/hematopoietic malignancies and autologous/allogeneic hematopoietic stem-cell transplantation (2C).

● CQ2 How should platelet transfusion be carried out in hematopoietic failure?

The platelet transfusion trigger in hematopoietic failure (patients with chronic hematopoietic failure such as aplastic anemia and myelodysplastic syndrome not receiving chemotherapy/hematopoietic stem-cell transplantation) should be set at 5,000/μL (2D).

● CQ3 How should platelet transfusion be carried out in treatments/surgeries in thrombocytopenic patients?

Central venous catheterization: If the platelet count before insertion of the central venous catheter is $<2\times10^4/\mu L$, platelet transfusion is performed to increase the platelet count to $\geq2\times10^4/\mu L$ before catheterization (2D).

Lumbar puncture: If the platelet count is ≤5×10^4/μL before lumbar puncture, platelet transfusion should be performed to increase the platelet count to ≥5×10^4/μL before puncture (2D).

Surgery: The platelet transfusion trigger before surgery is set at 5×10^4/μL, and a platelet count of 5×10^4/μL should be maintained until hemostasis is confirmed (2D).

● CQ4 How should platelet transfusion be carried out in idiopathic thrombocytopenic purpura?

The platelet increment of platelet transfusion is limited, and there is no indication for prophylactic platelet transfusion (2C). In active bleeding and surgery, difficulty in hemostasis is an indication for platelet transfusion (2C). Even in such situations, platelet transfusion should be considered after initiating treatments for idiopathic thrombocytopenic purpura such as steroids and immunoglobulin.

● CQ5 How should platelet transfusion be carried out in thrombotic thrombocytopenic purpura?

Prophylactic platelet transfusion should be avoided (2C). Although it is not contraindicated in the presence of active bleeding or during surgical treatment, it should be performed carefully and minimally with attention to the occurrence or exacerbation of thrombosis, as its safety has not been established.

● CQ6 How should platelet transfusion be carried out in heparin-induced thrombocytopenia?

In heparin-induced thrombocytopenia, prophylactic platelet transfusion should be

avoided since bleeding is rare because of the nature of the disorder (2C). It may be considered for active bleeding or surgery with a high risk of bleeding.

● CQ7 How should platelet transfusion be carried out in patients suspected to have platelet transfusion refractoriness due to immunological mechanisms?

If the corrected count increment (CCI) is low 10 minutes to 1 hour after the end of platelet transfusion, immune platelet transfusion refractoriness should be suspected (2C). If immune platelet transfusion refractoriness is suspected, the presence or absence of HLA antibody should be investigated (2C). If HLA antibodies are present, an HLA-compatible platelet concentrate should be used (1C). If an HLA-compatible platelet concentrate is used, the CCI is measured 10 minutes to 1 hour or 16-24 hours after the end of platelet transfusion, and the clinical efficacy is evaluated (1C).

● CQ8 What is the target platelet count when there is active bleeding?

If there is active bleeding, platelet transfusion should be performed, aiming to maintain the platelet count $\geq 5\times10^4/\mu L$ (2D). In the event of traumatic intracranial hemorrhage, platelet transfusion is performed, aiming to maintain the platelet count $\geq 10\times10^4/\mu L$ (2D).

Introduction

1. Objectives of preparation of the guidelines

The objective of the use of platelet concentrates is prevention (prophylactic platelet transfusion) and treatment (therapeutic platelet transfusion) of hemorrhage due to thrombocytopenia or platelet dysfunction.[1)] In patient blood management, securing the

safety of anticancer chemotherapy, surgery, treatment, and prevention/treatment of hemorrhage in thrombocytopenic patients, platelet concentrates are highly effective. However, platelet concentrates may induce adverse reactions, and not only fever and urticaria but also serious complications, such as anaphylaxis and transfusion-related acute lung injury. Alloantibodies may be induced by repeated platelet transfusion, resulting in immune platelet transfusion refractoriness. Therefore, it is necessary to use platelet concentrates as necessary, appropriately but minimally. Moreover, platelet concentrates are a precious resource based on the good will of donors and have a short shelf life. In particular, one should refrain from imprudently ordering unnecessary platelet concentrates that end up wasted.

The Guidelines for the Use of Blood Products, prepared by the Ministry of Health, Labour and Welfare (MHLW) to improve safety measures and promote the appropriate use of transfusion,[1)] are highly practical and are widely used in clinical practice. Recently, the Japan Society of Transfusion Medicine and Cell Therapy played a central role in the preparation of the current “Guidelines for the Use of Platelet Transfusion Concentrates based on Scientific Evidence” and determined recommendation grades based on scientific grounds (evidence) for more appropriate and proper use of blood products. In using the present guidelines, there are 4 points of attention: (1) The present guidelines are based on evidence from clinical trials, and are not guaranteed to be applicable to all patients under all clinical conditions. (2) In presenting the recommendation grades of clinical questions (CQs) and clinical conditions for which evidence is markedly deficient, reasons are mentioned as comments. (3) The present guidelines include recommendation grades/information to serve as a reference in using platelet concentrates, but unconditional compliance is not required. Whether the

guidelines should be followed or not should be assessed comprehensively and flexibly for each patient and each clinical circumstance. (4) Therefore, adherence or non-adherence to the guidelines herein is a matter of medical judgment rather than being a matter of law.

2. Circumstances of preparation

The preparation of these guidelines was initiated in November 2012 with the establishment of the Guidelines Revision Evaluation Committee of the Japan Society of Transfusion Medicine and Cell Therapy, and was taken over in 2013 by the Taskforce for Drafting of Guidelines for the Use of Platelet Concentrates, which is a subcommittee of the Guidelines Committee of the same society, and Study Concerning the Preparation of Evidence-based Transfusion Guidelines as a project funded by Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare. The members of the Taskforce for Drafting of Guidelines for the Use of Platelet Products were selected and approved by the administrative board of the Japan Society of Transfusion Medicine and Cell Therapy in May 2013 in consideration of their expertise.

3. Committee members and their roles (Table 1)

Japan Society of Transfusion Medicine and Cell Therapy

“Guidelines Revision Evaluation Committee”

Chairperson　Masanori Matsumoto　Nara Medical University

Project funded by Health and Labour Sciences Research Grants

“Study for Drafting of Evidence-based Guidelines for Transfusion”

Representative　Tadashi Matsumoto, Nagoya University

Japan Society of Transfusion Medicine and Cell Therapy, Guidelines Committee

Board member in charge: Yuji Yonemura, Kumamoto University.

Chairperson Masanori Matsumoto Nara Medical University

Taskforce for Drafting of Guidelines for the Use of Platelet Concentrates

Chairperson Akiyoshi Takami (formerly at) Kanazawa University (2010.11.-2014.2)
(presently at) Aichi Medical University (2014.3-)

Member Masao Ogata Oita University

Member (since 2015.5) Nobuharu Fujii Okayama University

Member Takaaki Hato Ehime University

Member Kubuki Yoko Miyazaki University

Member Shuichi Mizuta (formerly at) Fujita Health University (2015.5-2016.5)
(presently at) Toyohashi Medical Center (2016.6-)

Member (until 2015.5) Takehiro Kohno Osaka Medical College

Member (until 2015.5) Koji Matsuzaki Japanese Red Cross Society

Collaborator (since 2015.5) Yoshiaki Toyama Osaka University

4. Preparation method

CQs were set based on various sections of the Guidelines for the Use of Blood Products by the Ministry of Health, Labour and Welfare.[1)] From 7,871 papers in Japan and abroad concerning the use of platelet concentrates published in 1995-2014, 975 were selected primarily. Other important papers for the preparation of recommendation grades/comments (including papers published in and after 2015) were added as

hand-searched literature, and the evidence level and recommendation grade of each CQ were determined according to the Minds Handbook for Clinical Practice Guideline Development 2014.[2)] In the present guidelines, members were appointed to each CQ, and the chairperson of the taskforce supervised the appointed members. In evaluating the evidence in its entirety, 4 CQs were dropped (described below), and the evidence levels and recommendation grades are shown concerning the following 8 CQs.

5. List of CQs

CQ1 How should platelet transfusion be carried out in cancer/hematopoietic malignancies, and autologous/allogeneic hematopoietic stem cell transplantation?

CQ2 How should platelet transfusion be carried out in hematopoietic failure?

CQ3 How should platelet transfusion be carried out in treatments/surgeries in thrombocytopenic patients?

CQ4 How should platelet transfusion be carried out in idiopathic thrombocytopenic purpura?

CQ5 How should platelet transfusion be carried out in thrombotic thrombocytopenic purpura?

CQ6 How should platelet transfusion be carried out in heparin-induced thrombocytopenia?

CQ7 How should platelet transfusion be carried out in patients suspected to have platelet transfusion refractoriness due to immunological mechanisms?

CQ8 What is the target platelet count when there is active bleeding?

6. Literature retrieval (Table 2)

Important papers among those retrieved using each CQ as a keyword are presented. The initial draft was circulated for review within the taskforce. Public comments were invited through the web site of the society, and the final edition was prepared after modifications.

The evidence levels and recommendation grades are presented as, “1: Strongly recommended” or “2: Weakly recommended (proposed)”, following the Minds Handbook for Clinical Practice Guideline Development 2014.[2)] The strength of evidence (A, B, C, D) of the outcome in general is shown with the strength of recommendation.

A (strong): There is strong confidence in the estimate of the effect.
B (medium): There is moderate confidence in the estimate of the effect.
C (weak): The confidence in the estimate of the effect is limited.
D (very weak): There is little confidence in the estimate of the effect.

7. Release and revision

The present guidelines were published in the journal and on the web site of the Japan Society of Transfusion Medicine and Cell Therapy. Thereafter, guidelines will be revised periodically according to new scientific evidence.

8. Funding and conflicts of interest

Funds for the preparation of the present guidelines were derived from the Study for Drafting of Evidence-Based Transfusion Guidelines, which is a project sponsored by a Health and Labour Research Grant and a research and development project of the Japan

Agency for Medical Research and Development (AMED, representative: Tadashi Matsushita). Developers of the present guidelines have no vested interests in particular for-profit or non-profit organizations or pharmaceutical or medical equipment companies. Preparation Committee members made conflict of interest disclosures to the Japan Society of Transfusion Medicine and Cell Therapy, and the COI committee concluded that there were no conflicts of interest.

9. Types of platelet concentrates

For platelet transfusion, irradiated (Ir) and prestorage leukocyte reduced (LR) platelet concentrates (PC) (Ir-PC-LR) are used to prevent transfusion-associated graft-versus-host disease. Medical facilities may also purchase unirradiated preparations (PC-LR) from the Japan Red Cross Society and irradiate them in the facility before use. Domestic PC are all LR preparations, with target leukocyte counts $\leq 1\times10^6$ per bag (compliance rate: 95%). Ir-PC-LR preparations are available as 1-unit (20 mL, ¥7,875, 20 as of September 1, 2016; the same applies hereafter), 2-unit (40 mL, ¥15,749), 5-unit (100 mL, ¥40,100), 10-unit (200 mL, ¥79,875), 15-unit (250 mL, ¥119,800), and 20-unit (250 mL, ¥159,733; the same volume as a 15-unit preparation). To cope with platelet transfusion refractoriness associated with production of anti-HLA antibody, there are preparations obtained from HLA-compatible donors (Ir-PC-HLA-LR), and they are available as 10-unit (¥96,025), 15-unit (¥143,854), and 20-unit (¥191,496) preparations (with standard volumes the same as Ir-PC-LR). Platelet concentrates expire at 24:00 of Day 4, counting the day of collection as Day 1, rather than “4 days (96 hours) after collection.” Washed platelets are used to prevent allergic reactions after platelet transfusion. The expiration time of washed platelets is 48 hours after

preparation, but not beyond 24:00 on Day 4 after collection. Platelet concentrates are stored by agitation on a horizontal shaker at 20-24°C until use.

10. Effects of platelet concentrates

One unit of a platelet concentrate should contain $\geq 0.2\times10^{11}$ and $<0.4\times10^{11}$ platelets, corresponding to the number of platelets in 200 mL of whole blood, which can be calculated from a platelet count of $10\text{-}20\times10^4/\mu L$. When a platelet concentrate is administered, about one-third of the platelets are sequestered and destroyed in the spleen. Therefore, the platelet increment can be estimated as (the total number of transfused platelets ÷ circulating blood volume × 2 ÷ 3). By assuming the circulating blood volume as 7% of body weight and the dose of the platelet concentrate as 10 units, the estimated increase in platelet count is $0.2 \times 10^{11} \times 10 \div (\text{body weight [kg]} \times 0.07) \times 2 \div 3 = 4 \times 10^{11} \div \text{body weight [kg]} \times 0.21 = 2 \times 10^{12} \div \text{body weight [kg]} = 200 \times 10^{10} \div \text{body weight [kg]}$ (/L) $= 200 \times 10^4 \times 10^6 \div \text{body weight [kg]}$ ($/10^6$ μL) = 200 ÷ body weight [kg] ($\times10^4/\mu L$). For example, if the patient's body weight is 50 kg, preoperative platelet count is $2\times10^4/\mu L$, platelet transfusion trigger (see below) is $5\times10^4/\mu L$, expected operation time is 3 hours, and the surgery is endoscopic cholecystectomy, transfusion of 10 units of a platelet concentrate is expected to increase the platelet count by 200 ÷ 50 = $4\times10^4/\mu L$ to $6\times10^4/\mu L$. Therefore, it suffices to transfuse 10 units of a platelet concentrate preoperatively (usually arranged to finish transfusion 1 hour before surgery). Incidentally, 10 units of a platelet concentrate contain clotting factor activity equivalent to 1.7 units of fresh frozen plasma, excluding unstable clotting factors.

11. Platelet transfusion trigger vs. platelet transfusion target value

Conventionally, there have been two indices concerning the target platelet count in prophylactic platelet transfusion: the trigger (platelet count below which transfusion is performed) and target value (platelet count to meet or exceed through transfusion). If a target platelet count is pursued, the dose of platelet transfusion is more likely to increase. Clinically, the distinction between the two has been ambiguous. Exhaustively reviewing previous reports, we found research with high evidence levels favoring "trigger" over "target" transfusion, including the 6 randomized controlled trials (RCTs) deemed important for the present guidelines.[3-8] Even though nearly all these studies were conducted overseas, where availability of platelet concentrates differs from Japan, there are no reasonable grounds for adopting “target” transfusion practice. Therefore, “trigger” transfusion was adopted in the present guidelines. However, the following conditions must be taken into consideration: (1) In Japan, platelet concentrates are often provided by advance reservation, and their availability on the day of ordering is not guaranteed; (2) there are frequent consecutive holidays that interfere with measurement of the platelet count at a regular intervals; and (3) there are also some needs for platelet transfusion in remote areas. Therefore, the guidelines also accept the concept of the “predicted platelet transfusion trigger,” according to which platelet concentrates are ordered in advance by predicting the day on which the platelet count will decrease below the trigger, a modification of the original idea of a platelet transfusion trigger, in which platelet concentrates are ordered only after the platelet count has decreased below the target value, and transfusion is performed on the same day.

12. Limitations of evidence based on research reports

If relationships between the methods of platelet transfusion and serious outcomes (e.g., mortality rate) are demonstrated, the recommendation grades in the present guidelines are expected to be adjusted, but such research reports are few. For example, all 4 RCTs[3-6] that were extensively used in the preparation of the present guidelines evaluated the relationships between the methods of platelet transfusion (comparison of platelet transfusion trigger, etc.) and outcomes including the mortality rate, but it must be noted that patients with conditions such as active hemorrhage, fever, and clotting disorder, in whom platelets are likely to be consumed, and the risk of bleeding is increased, were excluded from the subjects.

13. Bleeding grades by the WHO bleeding scale (WHO bleeding grades) (Table 3)

In the present guidelines, importance was attached to the WHO bleeding scale (WHO bleeding grades) (see below),[9-11] which are widely used in clinical studies in Japan and abroad, in the outcome assessment. While there were no research reports in which the relationships between the WHO bleeding grades and clinical usefulness were evaluated, we attached importance to the fact that the outcome was evaluated according to the WHO bleeding grades in 5 RCTs referred to in the present guideline.[3-5,7,8]

14. Retraction of CQs

The following CQs were retracted after the secondary selection of the literature as a result of careful evaluation of the evidence, etc. The evidence levels and recommendation grades are shown concerning the remaining 8 CQs.

"Can the WHO bleeding grades be used for the assessment of hemorrhagic symptoms at the time of platelet transfusion?"

"Should the platelet count used for platelet transfusion be a trigger or target value?"

"How should platelet transfusion be carried out in patients with disseminating intravascular coagulation?"

"How should platelet transfusion be carried out in patients with platelet dysfunction (including that induced by drugs such as antiplatelet agents)?"

CQ1 How should platelet transfusion be carried out in cancer/hematopoietic malignancies, autologous/allogeneic hematopoietic stem cell transplantation?

Recommendation

The platelet transfusion trigger in chemotherapy for cancer/hematopoietic malignancies (other than acute promyelocytic leukemia) and autologous/allogeneic hematopoietic stem cell transplantation should be set at $1\times10^4/\mu L$ (2C). However, flexibility according to the patient's condition and medical care environment is necessary.

Platelet transfusion in chemotherapy for cancer/hematopoietic malignancies, autologous/allogeneic hematopoietic stem cell transfusion is performed prophylactically (2C).

Comment

In the preparation of the recommendation for this CQ, we placed the greatest emphasis on the results of 2 RCTs in which the platelet transfusion trigger after remission-induction chemotherapy in patients with adult acute leukemia (other than

acute promyelocytic leukemia) was compared (1×10^4/μL vs. 2×10^4/μL).[5,6] The platelet transfusion volume was significantly lower in the 1×10^4/μL group, but no significant difference was observed in the overall hemorrhage rate, serious hemorrhage rate, hemorrhage mortality rate, or necessary volume of red blood cell transfusion. Similar results were also obtained in a facility-based RCT in which the platelet transfusion triggers of 1×10^4 and 2×10^4/μL were assigned to facilities.[12] The results of a systematic review (SR) were also in agreement.[13] However, the overall evidence level of this CQ was limited to C (weak) in consideration of the results of a Cochrane review (SR) comparing platelet transfusion triggers of 1×10^4 and 2-3×10^4/μL,[14] i.e., inaccuracy was observed in the evidence concerning serious outcomes (e.g., the relative risk of hemorrhage mortality and 95% confidence interval in the first group were 2.67 and 0.11-64.91, respectively). The recommendation grade was proposed to be 2 (weakly recommended, because the balance between the benefit of the decrease in the platelet transfusion volume and the harm of promotion of hemorrhage was uncertain. Acute promyelocytic leukemia is discussed later. As a reference, there is a domestic retrospective study in 95 patients with acute leukemia other than those with acute promyelocytic leukemia and L3 by the FAB classification system,[15] which showed that the platelet transfusion volume was reduced without an increase in the risk of hemorrhage when the platelet transfusion trigger value in remission-induction therapy was changed from 2×10^4 /μL to 1-2×10^4/μL.

By an SR,[14] the risk of hemorrhage was reported to be lower in recipients of autologous hematopoietic cell transplantation than in leukemia patients during remission-induction therapy or recipients of allogeneic hematopoietic cell transplantation (relative risk: 0.73, 95% confidence interval: 0.65-0.82). Therefore,

there is no compelling reason for setting the platelet transfusion trigger higher in autologous hematopoietic stem cell transplantation than in leukemia patients undergoing remission-induction therapy, and we propose 1×10^4 /μL as a platelet transfusion trigger for autologous hematopoietic stem cell transplantation.

There is 1 RCT that compared platelet transfusion triggers of 1×10^4/μL (79 patients) and 3×10^4/μL (87 patients) in patients who received allogeneic hematopoietic cell transplantation,[16] reporting no significant post-transplant differences in outcome, overall hemorrhage rate, serious hemorrhage rate, or red blood cell transfusion volume. No deaths due to hemorrhage were observed in either group. The total number of transfused platelets was significantly reduced in the first group. In 2 SRs,[13,14] leukemia patients during remission-induction therapy and those receiving allogeneic hematopoietic stem cell transplantation were considered equivalent in terms of hemorrhagic risk. For these reasons, we also propose 1×10^4/μL as a platelet transfusion trigger in allogeneic hematopoietic cell transplantation. For reference, there is a report that retrospectively showed that the hemorrhagic risk is significantly increased within 100 days after bone marrow transplantation.[17] Actually, the platelet transfusion trigger is more often set at a higher level in allogeneic transplantation than after chemotherapy.[18] In allogeneic transplantation, in which complications such as organ injuries, infections, and fever are frequently observed, the possibility that a higher platelet transfusion trigger value is more likely to be selected empirically cannot be excluded for the reasons mentioned below. At any rate, the platelet transfusion trigger in patients receiving allogeneic transplantation should be determined with due regard for each patient's condition and medical care environment.

Since many of the reports used as the grounds for recommendation grades were

from abroad, particularly, Western countries, sufficient attention to the differences in the environment of platelet transfusion between Japan and abroad is necessary. Specifically, the following circumstances must be remembered: (1) in Japan, reservation is often required to procure platelet concentrates, and they are not necessarily available on the order date, (2) measurement of the platelet count at regular intervals is often difficult because of frequent consecutive holidays, and (3) there are also some needs for platelet transfusion in remote areas. Therefore, ordering platelet concentrates in advance by anticipating when the platelet count will fall below the trigger is permitted, instead of waiting for the platelet transfusion trigger before ordering, and performing platelet transfusion within the day. In addition, in 2 RCTs used as the grounds for the recommendation grades,[5,6] patients who were likely to bleed, such as those with active hemorrhage, fever, and clotting disorder are excluded, and it must be noted that the trials do not completely reflect every clinical reality.

Thrombocytopenia is considered to increase the risk of bleeding, but factors that induce bleeding in clinical situations other than the platelet count have been suggested. According to a retrospective observational study of 2,942 patients with thrombocytopenia at Johns Hopkins University,[17] clinical manifestations (uremia, hypoalbuminemia, recent hemorrhagic events, and recent bone marrow transplantation) significantly increased the risk of moderate or severe hemorrhage (WHO grade ≥2), but thrombocytopenia (platelet count in the morning, daily platelet nadir) showed no significant correlation with moderate or severe hemorrhage. This provokes controversy about the relative superiority/equivalence between conventional prophylactic platelet transfusion based on thrombocytopenia and therapeutic platelet transfusion based on the occurrence of minor hemorrhage. In 2 RCTs that compared prophylactic transfusion

with a platelet transfusion trigger of $1\times10^4/\mu L$ (same as our proposal) and therapeutic transfusion after minor hemorrhage,[3,4] there was no significant difference in the frequency of lethal bleeding by either approach. However, the frequency of WHO grade ≥2 hemorrhage was higher with the latter approach. In consideration of the inaccuracy of serious outcome evidence in an SR that included these studies,[13] the overall evidence level of this CQ was limited to C (weak). The benefit was considered to surpass the harm in terms of the cost and burden, although this judgment is based on overseas reports only. For these reasons, prophylactic transfusion is proposed at a recommendation grade of 2. Incidentally, there have been few reports that evaluated whether platelet transfusion affects serious outcomes (e.g., mortality rate) in thrombocytopenic patients. For reference, there is an observational study of 29 patients with acute leukemia conducted at the initiation of platelet transfusion,[19] reporting that platelet transfusion prevented lethal hemorrhage and improved the survival rate.

This recommendation does not mean that "a platelet count ≥$1\times10^4/\mu L$ is not an indication for platelet transfusion." Flexibity based on the patient's condition and medical care environment are necessary.[17,20] Overseas guidelines also adopt the same stance.[20-24] As an opinion of members of the preparation committee (expert opinion), a platelet transfusion trigger of $2\times10^4/\mu L$ is proposed, because an increase in the risk of hemorrhage cannot be excluded in the following events: An ongoing or recent episode of WHO grade 2 bleeding,[17,25,26] complications of liver disease accompanied by clotting abnormalities, complications of disseminated intravascular coagulation,[13,20] clinically unstable acute leukemia,[20] fever (sublingual temperature ≥38°C),[25-27] active infection (sepsis, febrile neutropenia, pneumonia, invasive aspergillosis, etc.),[20,25] ongoing anticoagulant therapy,[20,27] bladder cancer or necrotizing tumor to be treated,[20] ongoing

treatment with anti-thymocyte globulin, ongoing treatment using amphotericin,[20] a rapid decrease in the platelet count (a decrease of ≥2×10^4/μL in 3 days), leukocytosis (≥7.5×10^4/μL),[20,24] uremia,[17] hypoalbuminemia,[17] other pathological conditions in which platelet consumption is markedly enhanced, limited availability of platelet concentrates (before consecutive holidays, remote regions, after an earthquake or other disaster, etc.), before placement of a central venous catheter, headache, disturbance of consciousness, visual field impairment, and neurological symptoms., A platelet transfusion trigger value of 5×10^4/μL is proposed for the following events: an ongoing or recent episode of WHO grade 3 bleeding, and before intrathecal injection.

The risk of bleeding is usually high in acute promyelocytic leukemia before treatment.[20,24] As an expert opinion, we propose a platelet transfusion trigger of 2-5×10^4/μL according to clinical manifestations. The platelet transfusion triggers proposed in various clinical situations are: (1) 5×10^4/μL at the beginning of chemotherapy, at additional chemotherapy, and when it is complicated by differentiation syndrome, (2) 3×10^4/μL when it is complicated by disseminated intravascular coagulation, and (3) 1×10^4/μL when the condition is stable with improvement in hemorrhagic tendency (as in other acute leukemias). However, the evidence is extremely deficient, and recommendation grades are not shown.

In an RCT in the United States that examined the volume of a single prophylactic platelet transfusion for adult blood cancer (PLADO study),[7] no significant difference was observed in the frequency of WHO grade ≥2 bleeding among the groups transfused with platelets dosed at 1.1×10^{11}/m^2, 2.2×10^{11}/m^2, and 4.4×10^{11}/m^2 per transfusion. With increases in the number of platelets per transfusion, the number of transfusions

decreased, but the total number of platelets transfused increased. When the quantity of platelets transfused in this report, in which the mean body surface area was 1.9 mm^2, is scaled according to the Japanese mean body surface area of 1.6 mm^2, they correspond to 9, 18, and 35 units, respectively.[28] However, in an RCT in Canada (SToP study),[8] the outcome was compared between groups transfused with platelets at $1.5\text{-}2.9\times10^{11}/m^2$ (equivalent to 6-12 units in Japan) and $3.0\text{-}6.0\times10^{11}/m^2$ (equivalent to 13-25 units in Japan) per transfusion. While no significant difference was observed in the frequency of WHO grade ≥2 bleeding, the frequency of WHO grade 4 bleeding was significantly higher in the first group, and the study was discontinued before completion. In consideration of the fact that no validation has been made for Japan's domestic circumstances of blood donation, we only present a reference opinion that platelet transfusion of 10 units at a time, which is a common clinical practice in Japan, is reasonable, and make no proposal in terms of the number of units to be transfused at a time.

CQ2 How should platelet transfusion be carried out in hematopoietic failure?

Recommendation

For patients with hematopoietic failure (chronic hematopoietic failure such as aplastic anemia and myelodysplastic syndrome not treated by chemotherapy or hematopoietic stem cell transplantation), the platelet transfusion trigger is $\underline{0.5\times10^4/\mu L}$ (2D).

Comment

There have been few studies of the platelet transfusion trigger for patients with chronic hematopoietic failure such as aplastic anemia and myelodysplastic syndrome not treated by chemotherapy or hematopoietic stem cell transfusion. Moreover, there has been no study to evaluate a platelet trigger of $0.5\times10^4/\mu L$.

One prospective, observational study has been reported.[29] Subjects were 25 outpatients with severe aplastic anemia with platelet counts $\leq1\times10^4/\mu L$ (aged 15-76 years, median age: 43 years), and all of them had received immunosuppressive therapy at least once. The platelet transfusion trigger was: (1) $0.5\times10^4/\mu L$ if there was no extensive subcutaneous hemorrhage or serious bleeding (corresponding to WHO grade ≥2), fever $\geq38°C$ by a sublingual measurement, or clotting abnormality, and (2) $0.6\text{-}1\times10^4/\mu L$ if there was WHO grade ≥2 bleeding and/or fever, but (3) platelet transfusion was performed when there was WHO grade ≥3 bleeding or when mild surgery was expected even if the platelet count was $>1\times10^4/\mu L$. According to these principles, platelet transfusion was performed 1,135 times in an observation period of 18,706 patient-days (the platelet count was $\geq1\times10^4/\mu L$ in 88% and $\leq0.5\times10^4/\mu L$ in 57%), and the median interval between platelet transfusions was 10 days. Although 3 major hemorrhages were observed (gastrointestinal bleeding associated with angiodysplasia, retinal bleeding accompanied by misty vision, and intraperitoneal bleeding) during the observation period, they were all controlled by inpatient treatment (total duration of hospitalization: 19 days). Even by such restrictive transfusion policy, platelet transfusion refractoriness occurred in 4 patients due to alloantigen sensitization. It may be noted that these 4 patients eventually died due to hemorrhage after discontinuation of prophylactic platelet transfusion for reasons including the patient's wishes. Concerning

myelodysplastic syndrome, in a retrospective observational study of 2,900 patients,[30] a platelet count $<2\times10^4/\mu L$ was an independent risk factor of bleeding along with platelet anisocytosis, megakaryocytic hypoplasia, and megakaryocytic maturation disorder. In this report, there is no mention about effects of platelet transfusion on the risk of hemorrhage. However, it is difficult to recommend a platelet transfusion trigger above $0.5\times10^4/\mu L$ aiming at outcome improvements such as reduction of the risk of bleeding and improvement in the prognosis even when a patient with myelodysplastic syndrome has risk factors of bleeding such as platelet anisocytosis, megakaryocytic hypoplasia, megakaryocytic maturation disorder, and a platelet count $<2\times10^4/\mu L$. In consideration of the marked deficiency of (1) evidence concerning important outcomes and (2) domestic evidence, the recommendation grade of the trigger for hematopoietic failure in general was limited to 2D (proposed to be implemented but with little evidence).

As an expert opinion, a platelet transfusion trigger value of $1\times10^4/\mu L$ is proposed for conditions with increased platelet consumption (e.g., active hemorrhage, clotting abnormality, a fever of ≥38°C by sublingual measurement) (reference opinion). Empirically, there are cases of rapid decrease in the platelet count due to anti-thymocyte globulin therapy. As an expert opinion, a platelet transfusion trigger of $2\times10^4/\mu L$ is proposed for patients undergoing anti-thymocyte globulin therapy (reference opinion).

CQ3 How should platelet transfusion be carried out in treatments/surgeries in thrombocytopenic patients?

Recommendation

Central venous catheter placement: When the platelet count is $<2\times10^4/\mu L$ before central venous catheter placement, platelet transfusion is performed before catheterization, aiming for a platelet count of $\geq2\times10^4/\mu L$ (2D).

Lumbar puncture: When the platelet count is $\leq5\times10^4/\mu L$ before lumbar puncture, platelet transfusion is performed before puncture, aiming for a platelet count of $>5\times10^4/\mu L$ (2D).

Surgery: The platelet transfusion trigger before surgery is set at $5\times10^4/\mu L$, and a platelet count of $5\times10^4/\mu L$ is maintained until hemostasis is confirmed (2D).

Comment

Central venous catheter placement: There has been no study in which $2\times10^4/\mu L$ was evaluated as a platelet transfusion trigger in central venous catheter placement. In preparing the recommendation for this CQ, the greatest weight was attached to an observational study of 193 patients with leukemia (except acute promyelocytic leukemia) and 604 non-tunneled central venous catheter placements.[31] In elective central venous catheter placement by a skilled anesthesiologist or intensivist using the Seldinger technique, a platelet count $<2\times10^4/\mu L$ significantly increased the risk of bleeding. According to the report of an observational study of 105 fluoroscopic-guided central venous catheter placements,[32] platelet transfusion was performed during central venous catheterization if the platelet count was $<5\times10^4/\mu L$. No significant difference was observed in the frequency of complications among 3 groups including groups in which the platelet count before catheterization was $5\text{-}10\times10^4/\mu L$ and $>10\times10^4/\mu L$. By attaching greater importance to the first report, we propose platelet transfusion aiming

for a platelet count ≥2×10^4/μL before catheterization if the platelet count before catheterization is <2×10^4/μL (2D). There is also an SR[13] that supports this proposal. If the platelet count before central venous catheter placement is ≥2×10^4/μL and <5×10^4/μL, the indication for platelet transfusion should be evaluated due consideration of the patient's hemorrhagic tendency and general condition. As an expert opinion, platelet transfusion is usually unnecessary if the platelet count is ≥5×10^4/μL. It is important to note that acute promyelocytic leukemia was excluded in the report.[31] The platelet count at which central venous catheterization can be performed safely in patients with marked hemorrhagic tendency, such as those with acute promyelocytic leukemia and clotting abnormality, is unknown.

Lumbar puncture: There has been no study in which a platelet count of 5×10^4/μL was evaluated as a platelet transfusion trigger in lumbar puncture. In preparing the recommendation concerning this CQ, the greatest weight was attached to an observational study of 5,625 diagnostic or therapeutic lumbar punctures in 958 children with acute lymphocytic leukemia.[33] Thrombocytopenia was reported to be related to traumatic lumbar puncture (red blood cell count in cerebrospinal fluid: ≥10/μL) and bloody lumbar puncture (red blood cell count in cerebrospinal fluid: ≥500/μL). For reference, there is a report that traumatic puncture in diagnostic lumbar puncture was related to a poor prognosis in children with acute lymphocytic leukemia.[34] Using a platelet count of >10×10^4/μL (2,731 times, frequency of traumatic puncture: 25%) as a reference, the relative risk of traumatic puncture in thrombocytopenia (95% confidence interval) was 1.1 (0.8-1.5) with a platelet count of 7.6-10×10^4/μL (329 times, 34%), 1.2 (0.9-1.5) with a platelet count of 5.1-7.5×10^4/μL (494 times, 38%), 1.3 (1.1-1.6) with a

platelet count of 2.6-5×10^4/μL (638 times, 41%), and 1.5 (1.1-2.0) with a platelet count of 0.1-2.5×10^4/μL (371 times, 44%). Using a platelet count >10×10^4/μL (2,731 times, frequency of bloody puncture: 8%) as a reference, the relative risk (95% confidence interval) of bloody puncture in thrombocytopenia was 1.3 (0.9-2.0) with a platelet count of 7.6-10×10^4/μL (329 times, 14%), 1.3 (0.9-1.9) with a platelet count of 5.1-7.5×10^4/μL (494 times, 15%), 1.6 (1.2-2.1) with a platelet count of 2.6-5×10^4/μL (638 times, 18%), and 1.6 (1.1-2.3) with a platelet count of 0.1-2.5×10^4/μL (371 times, 18%). From these results, a platelet count ≤5×10^4/μL is considered to be a significant risk factor of traumatic/bloody puncture. An observational study of the same 958 patients with 5,442 diagnostic or therapeutic lumbar punctures[35] was also used as a reference. The 95% confidence interval for the incidence of serious complications (nerve injury, infection, or hemorrhage) after lumbar puncture was 0-0.07% at a platelet count >10×10^4/μL (3,424 times), 0-0.40% at a platelet count of 5.1-10×10^4/μL (858 times), 0-1.27% at a platelet count of 4.1-5.0×10^4/μL (273 times), 0-1.48% at a platelet count of 3.1-4.0×10^4/μL (235 times) 0-1.49% at a platelet count of 2.1-3.0×10^4/μL (234 times), and 0-1.75% at a platelet count ≤2×10^4/μL (199 times). While no significant difference was observed, the upper limit of the 95% confidence interval tended to be higher in the groups with a platelet count ≤5×10^4/μL. From these results, we propose platelet transfusion aiming for a platelet count >5×10^4/μL before puncture if the platelet count is ≤5×10^4/μL before lumbar puncture (2D). However, there have been few reports that evaluated the effects of platelet count in lumbar puncture, and there has been no SR or RCT. Among 54 children with blood cancers, 738 therapeutic lumbar punctures had no serious complications in the group with a platelet count of 3.1-5×10^4/μL (27 times), and

the risk of traumatic/bloody puncture was reported to be comparable to that in the group with a platelet count >5×10^4/μL (711 times).[36] Conversely, the possibility that the risk of bleeding after lumbar puncture is increased in patients with clotting abnormalities, hemorrhagic tendency, or who are otherwise unstable cannot be excluded. Therefore, indications for platelet transfusion should be evaluated individually. Concerning indications for platelet transfusion in therapeutic lumbar spinal anesthesia such as epidural anesthesia, the evidence is limited, and no proposal is made.

Surgery: There are 2 observational studies in which the relationship between preoperative thrombocytopenia and postoperative outcome was evaluated.[37,38] Among 6,321 adult inpatients who underwent platelet transfusion (64% of all inpatients in Finland), 442 (13.1%) of 3,399 who underwent surgery died in the hospital, and the hospital mortality was higher compared with 158 deaths (5.4%) in 2,922 non-surgical patients.[38] At the University of Maryland Cancer Center, invasive treatments including 29 major surgeries (as defined by the authors: 13 laparotomies, 9 craniotomies, 4 thoracotomies, 1 femoral head replacement, 1 above-the-knee amputation, and 1 orchiectomy) were carried out 167 times at a preoperative platelet count <10×10^4/μL in 95 patients with acute leukemia.[37] In 130 surgeries performed at a preoperative platelet count <5×10^4/μL, platelet transfusion was performed, aiming for a platelet count ≥5×10^4/μL. Platelet transfusion was performed to maintain the platelet count ≥4×10^4/μL for 3 days after major surgeries and ≥3×10^4/μL for 3 days after other invasive treatments. While the volume of hemorrhage during surgery was >500 mL in 7% of invasive treatments, there was no death due to hemorrhage related to invasive treatments. The risk factors of intraoperative/postoperative massive bleeding (volume of intraoperative hemorrhage >500 mL or intraoperative/postoperative red blood cell transfusion >4

units) were major surgery, preoperative fever, and preoperative clotting disorder, and the preoperative platelet count was not a significant risk factor. There are no reports that evaluated the relationship between a preoperative platelet count $<5\times10^4/\mu L$ and postoperative outcome. There are also no reports that massive bleeding increases when the intraoperative platelet count was $\geq5\times10^4/\mu L$ or reports that support the usefulness of a preoperative platelet transfusion trigger value $>5\times10^4/\mu L$ (e.g., $7\text{-}10\times10^4/\mu L$). As an expert opinion, we propose $5\times10^4/\mu L$ as a platelet transfusion trigger before surgery and to maintain a platelet count of $5\times10^4/\mu L$ until hemostasis is confirmed, at a low recommendation grade. However, surgeries considered to be associated with a high risk of bleeding, such as brain and spinal cord surgery (except local eye surgeries such as lens replacement for cataract and retinal surgery), coronary artery/cardiovascular bypass surgery, surgery of major cardiac blood vessels using cardiopulmonary bypass, surgery that requires extensive adhesiolysis, and surgeries in patients with chronic kidney disease or liver disease with hemorrhagic tendency, are excluded. The evidence concerning these conditions is extremely deficient, and the recommendation grade for the target platelet count is not shown. Although this report does not affect the recommendation as it appeared after a secondary search of the literature, preoperative platelet transfusion (71 cases) was associated with more days in the ICU specifically, and in the hospital generally, without reducing the amount to perioperative red blood cell transfusion, by a propensity analysis of 870 cases of non-cardiac surgery in adults with a preoperative platelet count $<10\times10^4/\mu L$.[39] Although the reason that platelet transfusion adversely affects the clinical course is unclear, transfusion complications such as fever, hemolysis, anaphylaxis, and transfusion-related acute lung injury have

been suggested. Since there was no mention about the preoperative platelet count, the effects of the preoperative platelet count are unknown, but this report is considered to support avoidance of increasing the platelet transfusion trigger before surgery to $10\times10^4/\mu L$. Incidentally, if alternatives to platelet transfusion are available (e.g., in diseases for which thrombopoietin receptor agonists are indicated), their use should also be considered.

Others: Empirically, prophylactic platelet transfusion is usually unnecessary for bone marrow examinations (including biopsy) in which hemostasis by compression is possible (reference opinion). Empirically, prophylactic platelet transfusion is also unnecessary for tooth extraction, but platelet transfusion aiming for a platelet count $\geq1\times10^4/\mu L$ can also be performed (reference opinion). There have been few reports concerning the effects of thrombocytopenia on the outcome of gastrointestinal endoscopy, bronchoscopy, or needle biopsy, and recommendation grades of platelet transfusion in these procedures are not shown.

CQ4 How should platelet transfusion be carried out in idiopathic thrombocytopenic purpura?

Recommendation

The platelet-increasing effect of platelet transfusion is limited, and there is no indication for prophylactic platelet transfusion (2C). In active hemorrhage and surgery, difficulty in hemostasis is an indication for platelet transfusion (2C). Even in such events, the use of platelet transfusion should be considered only after initiating treatments for idiopathic thrombocytopenic purpura such as steroids and

immunoglobulin.

Comment

Platelet transfusion is usually not expected to be effective in idiopathic thrombocytopenic purpura. In addition, there is no evidence that platelet transfusion reduces the mortality rate/hemorrhage rate. Therefore, there is usually no indication for prophylactic platelet transfusion.

Active hemorrhage and surgery are indications for platelet transfusion, but there is a report that the platelet count was sufficiently increased by platelet transfusion during high-dose immunoglobulin administration,[40] and its use should be considered in combination with treatments for the primary disease. Whether platelet transfusion is necessary or not in laparoscopic splenectomy for idiopathic thrombocytopenic purpura is controversial,[41,42] so decisions must individualized for each patient.

Since there is no evidence that platelet transfusion increases the risk of thrombosis in this disease,[43] platelet transfusion may be ordered by a physicians mindful of the limitations of its effect, if it is judged to be necessary for the management of active hemorrhage or in surgery.

CQ5 How should platelet transfusion be carried out in thrombotic thrombocytopenic purpura?

Recommendation

Prophylactic platelet transfusion should be avoided (2C). Although it is not contraindicated for ongoing active hemorrhage or surgery, it should be performed

carefully and minimally with attention to the occurrence or exacerbation of thrombosis, as its safety has not been confirmed.

Comment

There have been a number of reports concerning whether platelet transfusion for thrombotic thrombocytopenic purpura induces thrombosis or not, and no decisive conclusion has been reached.

In an SR reported in 2009,[44] no difference was observed in the incidence of thrombosis or death regardless of whether platelet transfusion was performed or not, and it was concluded that the harm of platelet supplementation was unclear. Moreover, there was a report in 2015 that no thrombosis was observed in 19 patients with thrombotic thrombocytopenic purpura who underwent platelet transfusion.[45] On the other hand, according to an exhaustive retrospective study across the United States that analyzed a database of 10,000 patients identified by insurance coding as having thrombotic thrombocytopenic purpura,[43] platelet transfusion increased arterial thrombosis, acute myocardial infarction, and mortality rate. We attached importance to this study because of its large scale and exhaustiveness despite its retrospective design.

There are also positive and negative opinions about platelet transfusion in plasma exchange, which is the most important treatment for thrombotic thrombocytopenic purpura. While there is a report that no clear adverse effect was noted by platelet transfusion before catheterization for plasma exchange,[46] lethal thrombosis has also been reported.[47] Concerning platelet transfusion after the initiation of plasma exchange, no thrombotic event was reported to have occurred.[48] At any rate, it is necessary to perform platelet transfusion carefully and minimally.

CQ6 How should platelet transfusion be carried out in heparin-induced thrombocytopenia?

Recommendation

Since bleeding is rare in heparin-induced thrombocytopenia because of the nature of the disorder, prophylactic platelet transfusion should be avoided (2C). It may be considered in the event of active hemorrhage or surgery with a high risk of bleeding.

Comment

Classically, many guidelines regard heparin-induced thrombocytopenia as a contraindication for platelet transfusion, but this view is often based on case reports, and whether platelet transfusion increases the incidence of thrombosis remains open. In the United States, analysis of databases of a large number of patients identified by insurance coding as having heparin-induced thrombocytopenia concluded that platelet transfusion increases the incidence of arterial thrombosis and mortality rate.[43] Since the reliability of the diagnosis and temporal relationship between platelet transfusion and the occurrence of thrombosis are unclear, direct evidence is insufficient.

As a reference, there are reports that platelet transfusion could be performed safely, but they are retrospective reports of a small number of cases[49] or case reports,[50] and evidence indicating safety is also deficient. In consideration of the rareness of hemorrhage due to the nature of heparin-induced thrombocytopenia, it is necessary to perform platelet transfusion carefully and minimally.

CQ7 How should platelet transfusion be carried out in patients suspected to have platelet transfusion refractoriness due to immunological mechanisms?

Recommendation

If the corrected count increment (CCI) is low 10 minutes to 1 hour after the end of platelet transfusion, immune platelet transfusion refractoriness is suspected (2C). If immune platelet transfusion refractoriness is suspected, the presence or absence of HLA antibody is checked (2C). If HLA antibodies are present, HLA-compatible platelet concentrates are used (1C). The CCI is examined 10 minutes to 1 hour or 16-24 hours after HLA-compatible platelet transfusion to assess its clinical efficacy (1C).

Comment

Platelet transfusion refractoriness is a state in which platelet transfusion fails to produce a sufficient effect. Platelet transfusion refractoriness may be caused by immune factors, such as HLA or human platelet antigen (HPA) antibodies, or non-immune factors. Platelet transfusion refractoriness is diagnosed using the formula: Corrected count increment (CCI) [/μL] = (platelet count after transfusion [/μL] – platelet count before transfusion [/μL]) × body surface area [m^2] ÷ total number of platelets transfused [$\times 10^{11}$]. (Note the total number of platelets transfused, the denominator, is 2 Western units when a platelet concentrate of 10 Japanese units is transfused.[1,51-53]) The body surface area (m^2) is calculated as the height$^{0.725}$ × body weight$^{0.425}$ × 71.8/10000.[54] Usually, a diagnosis of platelet transfusion refractoriness is made when the CCI 16-24 hours after transfusion is <4,500/μL.[24,55] Moreover, the CCI at 10 minutes to 1 hour after the end of platelet transfusion is measured, and immune

platelet transfusion refractoriness is suspected if it is <7,500/μL.[24,51,55] Empirically, sensitivity of the CCI for the diagnosis of immune platelet transfusion refractoriness is high,[55,56] but there was no report in which the specificity was evaluated statistically. Non-immune platelet transfusion refractoriness cannot be excluded even when the CCI 10 minutes to 1 hour after the end of platelet transfusion is low. In observational studies,[52,57] HLA antibody testing proceeded when immune platelet transfusion refractoriness was suspected from a low CCI at 10 minutes to 1 hour after the end of platelet transfusion, and HLA-compatible platelet concentrates were useful if HLA antibodies were detected, so their use is proposed. If HLA antibody screening is negative, HPA antibody testing is performed. Observational studies of a small number of subjects[58,59] suggest that, if HPA antibodies are detected, HPA-compatible platelet concentrates are expected to be effective (a report by Kopko et al., which appeared after the secondary search of the literature, does not affect the recommendation), and this approach is proposed. However, HPA antibodies and HLA antibodies are often simultaneously detected, and the evidence concerning whether positive HPA antibody alone can be a cause of platelet transfusion refractoriness is deficient.[57] Therefore, the recommendation grade concerning the use of HPA-compatible platelet concentrates is not presented. Also, as the testing method or cut-off value of HLA (or HPA) antibody has not been standardized, there is the possibility that the antibody test may be falsely positive or negative. Therefore, if HLA (or HPA)-compatible platelet concentrates are used, the clinical effects of platelet transfusion should be checked. For this purpose, the evaluation of the clinical efficacy according to a CCI at 10 minutes to 1 hour or 16-24 hours after the end of platelet transfusion is strongly recommended (1C). Causes of non-immune platelet transfusion refractoriness include idiopathic thrombocytopenic

purpura, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia, disseminated intravascular coagulation, hypersplenism, fever, infection, hemorrhage, and drugs (including amphotericin).[60,61)]

Pre-storage leukocyte reduction has been reported to be effective for the prevention of immune platelet transfusion refractoriness.[62,63)] After introducing pre-storage leukocyte-reduced preparations, the use of HLA-compatible platelet concentrates has decreased markedly overseas.[64)] However, the amount of HLA-compatible platelet concentrates used in Japan has been increasing annually even following the wide availability of pre-storage leukocyte-reduced preparations. In addition, the efficacy rate of HLA-compatible platelet concentrates is low at 34% according to assessments using the CCI.[65)] Even if HLA (or HPA) antibody is judged to be negative, the possibility of thrombocytopenia due to immune mechanisms cannot be excluded because of the problem of sensitivity. However, without improvement in the CCI after HLA (or HPA)-compatible platelet transfusion, the effect of immune platelet transfusion refractoriness is uncertain, and the involvement of non-immune mechanisms should be considered. In such an event, HLA (or HPA)-compatible platelet concentrates are considered unlikely to be effective, but this view lacks evidence, and the recommendation grade is not shown. Incidentally, as immune platelet transfusion refractoriness is often caused by the patient's HLA-A or HLA-B antibodies, platelet concentrates compatible with the patient's HLA-A and HLA-B types are used for transfusion.[58)] There is an observational study that 7% (6 of 88) blood cancer patients with HLA antibody-related immune platelet transfusion refractoriness had immune platelet transfusion refractoriness due to HLA-C antibody,[66)] and the effect of immune platelet transfusion refractoriness cannot be excluded even when no improvement in the

CCI is observed after HLA-compatible platelet transfusion.

In HLA-compatible platelet transfusion, ABO-incompatible platelet concentrates may be used if ABO-identical blood is difficult to obtain. In this event, attention to the possibility of hemolysis due to anti-A or anti-B antibody is necessary. However, hemolytic adverse reactions are often caused by preparations derived from type O blood.[67] If the anti-A or anti-B antibody level in the ABO-incompatible platelet concentrate to be used is ≥128, the use of washed platelets is favored.[68] (Partial revision of the Guidelines for the Use of Blood Products, June 14, 2016; Notification No. 0614-1 issued by the Director of Pharmaceutical Safety and Environmental Health Bureau). Also, if the patient's anti-A or anti-B antibody level is high (usually ≥128), ABO-incompatible platelet concentrates may not be expected to be effective.[69] Since a very large burden is imposed on particular donors to secure the supply of HLA (or HPA)-compatible platelet transfusion preparations, appropriate and careful judgments are imperative for reasons beyond the immediate needs of a particular patient.

CQ8 What is the target platelet count when there is active bleeding?

Recommendation

If active hemorrhage is present, platelet transfusion is performed, aiming to maintain the platelet count $\geq 5\times10^4/\mu L$ (2D). In traumatic intracranial hemorrhage, platelet transfusion is performed, aiming to maintain the platelet count at $10\times10^4/\mu L$ (2D).

Comment

This CQ is intended for thrombocytopenic patients with relatively severe (corresponding to WHO grade ≥2) active bleeding. A search was made for research reports concerning conditions including gastrointestinal bleeding, cerebral hemorrhage, and massive bleeding and the platelet transfusion trigger value.

In an SR that evaluated the platelet transfusion trigger for non-variceal upper gastrointestinal bleeding in thrombocytopenia,[70] reports of 18 studies including 4 RCTs and 6 cohort studies were analyzed. No report with a high evidence level useful for the determination of the platelet transfusion trigger was shown to exist. However, by expert consensus, $5\times10^4/\mu L$ was proposed as a platelet transfusion trigger (equivalent to 2D).

In an observational study of 36 patients who received massive transfusion,[71] a platelet count $\geq5\times10^4/\mu L$ was reported to be necessary to prevent microvascular bleeding. In another prospective observational study of 27 patients who received massive transfusion, a platelet count $\geq10\times10^4/\mu L$ was reported to be necessary to prevent diffuse bleeding.[72] Based on these reports, English guidelines[73] recommend maintaining the platelet count $\geq5\times10^4/\mu L$ in patients with active bleeding. This approach is also recommended in guidelines of the Ministry of Health, Labour and Welfare[1] (no evidence is shown; considered an empirical recommendation). English guidelines further recommend maintenance of the platelet count $\geq10\times10^4/\mu L$ in the event of multiple trauma, brain injury, and massive bleeding.[73,74] For reference, a platelet count $<10\times10^4/\mu L$ was also a significant poor prognostic factor in a retrospective observational study of 626 patients with traumatic intracranial hemorrhage.[75] Based on these reports, an SR[76] recommends that the platelet count should be maintained $\geq5\times10^4/\mu L$ in traumatic hemorrhage and at $10\times10^4/\mu L$ in continuous bleeding or

traumatic cerebral hemorrhage. There is no mention about platelet transfusion in active bleeding in the latest guidelines from AABB (formerly, the American Association of Blood Banks).[11] There was no research report on the platelet transfusion trigger concerning cerebral hemorrhage with thrombocytopenia. For these reasons, the overall evidence level was limited to D (very weak).

As observed above, evidence concerning this CQ is deficient, but the evidence level was set at 2 as an expert opinion in consideration of the usefulness of the procedure in actual clinical settings. By attaching importance to the SR concerning non-variceal upper gastrointestinal bleeding with thrombocytopenia[70] and an observational study of 36 patients concerning microvascular hemorrhage,[71] a platelet count $\geq 5\times10^4/\mu L$ is proposed as a target in active hemorrhage. By attaching importance to an evaluation of 626 patients with traumatic intracranial hemorrhage,[75] although it is a retrospective observational study, a platelet count of $10\times10^4/\mu L$ is proposed as a target in traumatic intracranial hemorrhage. In setting the target platelet count, opinions of the guideline committee (which includes cardiovascular surgeons and emergency care physicians) and experience were used as references.

An RCT concerning intracranial hemorrhage associated with antiplatelet therapy at a platelet count $\geq 10\times10^4/\mu L$[77] showed an increase in the mortality rate due to platelet transfusion. However, this RCT, which was reported after secondary screening of the literature, was not included in the recommendation.

Since hemostasis cannot be achieved in active bleeding by platelet transfusion without hemostatic treatment, priority should be placed on hemostasis at the site of hemorrhage. No recommendation is shown in the present guidelines for platelet transfusion in massive bleeding, because the Guidelines for Critical Bleeding is being

prepared separately. A platelet count ≥$10\times10^4/\mu L$ after massive bleeding is a favorable prognostic factor.[72,78)] However, it is difficult to achieve a platelet count of $10\times10^4/\mu L$ by platelet transfusion because of thrombocytopenia due to massive bleeding, and it should not be set as a target value. In massive bleeding, opportunities to judge whether platelet transfusion can be based on a platelet count are considered to be limited.