Impressive tissue regeneration of severe oral mucositis post stem cell transplantation using cord blood platelet gel

Andrea Piccin,[1,2,3,4] Paolo Rebulla,[5] Simonetta Pupella,[6] Mario Tagnin,[7] Giuseppe Marano,[6] Angela Maria Di Pierro,[1,4] Michele Santodirocco,[8] Lazzaro Di Mauro,[8] Lisa Beqiri,[7] Michael Kob,[2,4] Marco Primerano,[4,9] Marco Casini,[1] Atto Billio,[1] Klaus Eisendle,[2,4,10] and Fabrizio Fontanella[4,7]

BACKGROUND: Platelet gel from cord blood (CBPG) is a recently developed blood component for topical use. We report a case of life-threatening mucositis after high-dose chemotherapy with fotemustine and cytarabine that was successfully treated with CBPG.

CASE REPORT: A patient with non-Hodgkin lymphoma who was undergoing autologous hematopoietic stem cell transplantation developed severe oral and esophageal mucositis with severe bacterial sepsis and cytomegalovirus infection, causing prolonged neutropenia. CBPG was topically administered daily to the oral cavity. The CBPG was partially reabsorbed and partially swallowed.

RESULTS: After 8 consecutive days of administration, the patient's oral mucosa markedly improved, showing restitutio ad integrum, and the patient's clinical status progressively improved. No side effects were seen after CBPG application.

CONCLUSION: This case supports the need to conduct controlled studies comparing the efficacy of autologous and allogeneic platelet gel from adult and umbilical cord blood for the topical treatment of severe oral mucositis occurring after high-dose chemotherapy.

Oral mucositis is a severe complication of chemotherapy and radiotherapy in patients who require hematopoietic stem cell transplantation (HSCT).[1] It is characterized by ulcerative lesions of oral mucosa that are very painful and can significantly compromise nutrition, mouth care, and quality of life.[2] Patients with mucositis have an increased risk of local and systemic infection that can cause sepsis, particularly during periods of profound immunosuppression.[3,4] The management of oral mucositis usually involves the use of several topical symptomatic drugs that may be only partially beneficial. According to oral oncology guidelines, although considerable progress has been made in the

ABBREVIATIONS: CBPG = cord blood platelet gel; HSCT = hematopoietic stem cell transplantation.

From the [1]Hematology Department, San Maurizio Regional Hospital, South Tyrol, Italy; the [2]Claudiana College of Healthcare Professions, Bolzano, South Tyrol, Italy; [3]Internal Medicine V, University of Innsbruck, Innsbruck, Austria; the [4]IMREST, Interdisciplinary Medical Research Center of South Tyrol, Bolzano South Tyrol, Italy; the [5]Blood Transfusion Center, Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; the [6]Istituto Superiore di Sanità, Italian National Blood Center, Rome, Italy; the [7]Odontostomatology Department, San Maurizio Regional Hospital, South Tyrol, Italy; the [8]Puglia Cord Blood Bank, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; and the [9]Hospital Pharmacy, San Maurizio Regional Hospital; and the [10]Department of Dermatology, Venerology, and Allergology, San Maurizio Regional Hospital, South Tyrol, Italy.

Address reprint requests to: Andrea Piccin, Hematology Department, San Maurizio Regional Hospital, 39100 Bolzano, South Tyrol, Italy; e-mail: apiccin@gmail.com

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treatment of oral mucositis, additional and sustained efforts are required to achieve optimal therapeutic strategies.[5]

Previous studies have reported on the successful use of allogeneic platelet gel obtained from adult blood donors for the treatment of oral mucositis induced by radiotherapy[6] and in a pediatric case of mucositis after chemotherapy.[7] Platelet gel from cord blood (CBPG), a recently developed allogeneic blood component for topical use, may represent a new treatment for mucositis because of its high content of microRNA and growth factors. No conclusive evidence is available with regard to a specific pathophysiologic mechanism that would make cord blood–derived platelets preferable to those obtained from adult blood. However, proteomic studies have outlined differences in the proteome of adult versus cord blood platelets, which indicate greater anti-inflammatory properties in the latter.[8]

During wound-healing processes, platelet-derived growth factors stimulate tissue repair and cell proliferation, influence extracellular matrix deposition, and support cell proliferation and differentiation. Moreover, platelet gel has an analgesic function and can reduce neurologic and neuropathic pain associated with wounds. Recently, our group reported on two cases of severe chronic wounds (skin radiodermatitis, soft tissue wound of the neck, and jaw osteoradionecrosis) that failed to heal using standard treatments but were successfully treated by CBPG.[9,10] This positive clinical response prompted us to use CBPG for the topical treatment of oral mucositis in a patient undergoing HSCT.

CASE DESCRIPTION

We report on a 68-year-old woman who first came to our institution in December 2015 because of a laterocervicalis lymphadenopathy swelling 3 × 3 cm in size. Both histologic and immunohistochemistry studies were in keeping with a diagnosis of mantle cell non-Hodgkin's lymphoma, pleomorphic variant (CD20+, CD5+, BCL-1+, CD10+, weak positivity for BCL-6; KI 67 index, 20-60%). In March 2016, the patient received a first cycle of chemotherapy (R-DHAOX [rituximab, dexamethasone, high-dose cytarabine, and oxaliplatin]). She received a second cycle in April 2016, followed by peripheral blood stem cell collection. After May 2016, she received four cycles of bendamustine plus rituximab; and, on September 22, 2016, she underwent autologous HSCT with the FEAM regimen (fotemustine plus etoposide, cytarabine, and melphalan). In total, 5.2×10^6 CD34+ cells were infused. The full blood count reached the nadir on September 29, and her aplasia resolved on October 10 (neutrophil count >500/μL, platelets count >20.000/μL). During aplasia, she spiked a temperature greater than 38°C, and she was treated with broad-spectrum antibiotics (piperacillin tazobactam and vancomycin). On October 13, she developed disseminated intravascular coagulation with septic shock and respiratory failure, requiring admission to the intensive care unit for 10 days. Vancomycin and acyclovir were given empirically; and, although she recovered well from the septic shock episode, on October 28, she developed grade IV oropharyngeal mucositis with impaired alimentation capacity.

We processed cord blood into platelet gel in compliance with the Italian recommendations provided by the Italian Society of Transfusion Medicine and Immunohaematology on "topical blood components for non-transfusional use."[11] CBPG was prepared according to a previously reported protocol[12] and was administered daily in early November for 7 days. The patient was asked to place the CBPG in her mouth cavity and to distribute it with her tongue on the inside mucosa. The gel was rapidly absorbed and also partially swallowed. A significant improvement in mucositis and pain was noted after only 3 days of consecutive application. On Day 8, restituto ad integrum of her mucosa was noted (Fig. 1). Furthermore, in association with mucosal healing, the trend of lymphocytes immediately after CBPG application showed a peak, which was not observed for the total white cell count or for neutrophils (Fig. 2). No clinical complications were recorded. A blood culture on November 2 was positive for cytomegalovirus (CMV) by polymerase chain reaction, with 5.5×10^6 copies, and the patient was immediately started on intravenous foscarnet sodium (Foscavir; Pfizer, Inc.) until November 11, when her blood cultures became negative. The patient's general condition slowly improved and, 3 weeks later, she was discharged from hospital.

CBPG PREPARATION

A detailed procedure for the preparation of CBPG has been reported elsewhere.[12] Briefly, cord blood units are collected in plastic bags containing 30 mL anticoagulant citrate-phosphate-dextrose-adenine solution by trained midwives according to standard procedures for public cord blood banking. Units containing less than 1.5×10^9 nucleated cells (which are not routinely banked for allogeneic hematopoietic transplantation purposes), a platelet count of 150×10^9/L or greater, and a volume of 50 mL or greater are processed into CBPG within 48 hours of collection by blood bank staff. The units are centrifuged at 200 to 210 × *g* for 10 to 15 minutes, and the platelet-rich plasma is collected in a transfer bag, which is centrifuged at 1800 to 2600 × *g* for 15 minutes. Most of the supernatant platelet-poor plasma is then removed, and the platelets are resuspended at a concentration of $1 \pm 0.2 \times 10^6$/μL. The platelet concentrate, with an average volume of approximately 10 mL, is finally transferred into a storage bag and cryopreserved without cryoprotectant in a mechanical freezer at a temperature below −40°C. At the time of use, the platelet concentrate is thawed, and a

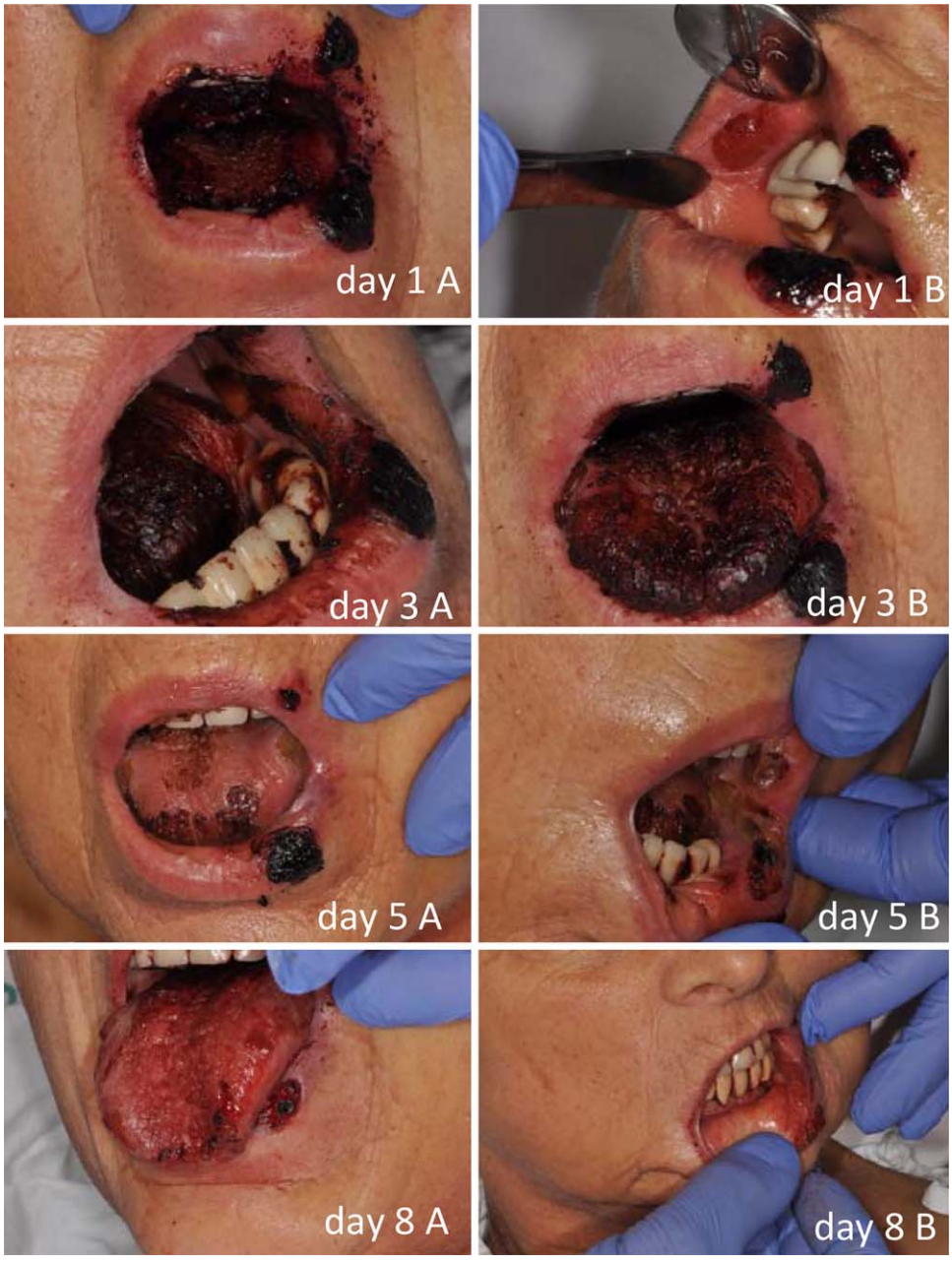

Fig. 1. (Day 1A,B) Difficulty with fully opening the mouth and protruding the tongue. (Day 3A,B) The mouth can open slightly more, and the tongue tip can be seen. Necrotic tissue is reduced. Speaking also was improved. (Day 5A,B) The patient can fully extrude her tongue, and there are clear signs of regeneration (tongue redness). (Day 8A,B) Clear improvement is observed, and the patient can fully extrude her tongue. [Color figure can be viewed at wileyonlinelibrary.com]

platelet gel is formed by the addition of 10% calcium gluconate in a 1:3 ratio (3 mL calcium gluconate per 9 mL platelet concentrate).

DISCUSSION

Severe oral mucositis remains a serious complication for patients undergoing HSCT and chemotherapies, and its treatment is often very challenging. The risk of developing infections is very high because of the natural presence of bacteria within the oral cavity. Our patient developed a classical Gram-positive infection (*Streptococcus mitis*) and a further infection with CMV. The FEAM regimen used here has been associated with grade III mucositis in up to 23% of cases.[13] Previous studies on platelet gel have shown that it not only favors tissue regeneration but also reduces pain and controls infection. We observed that the general performance status of our patient showed a clear

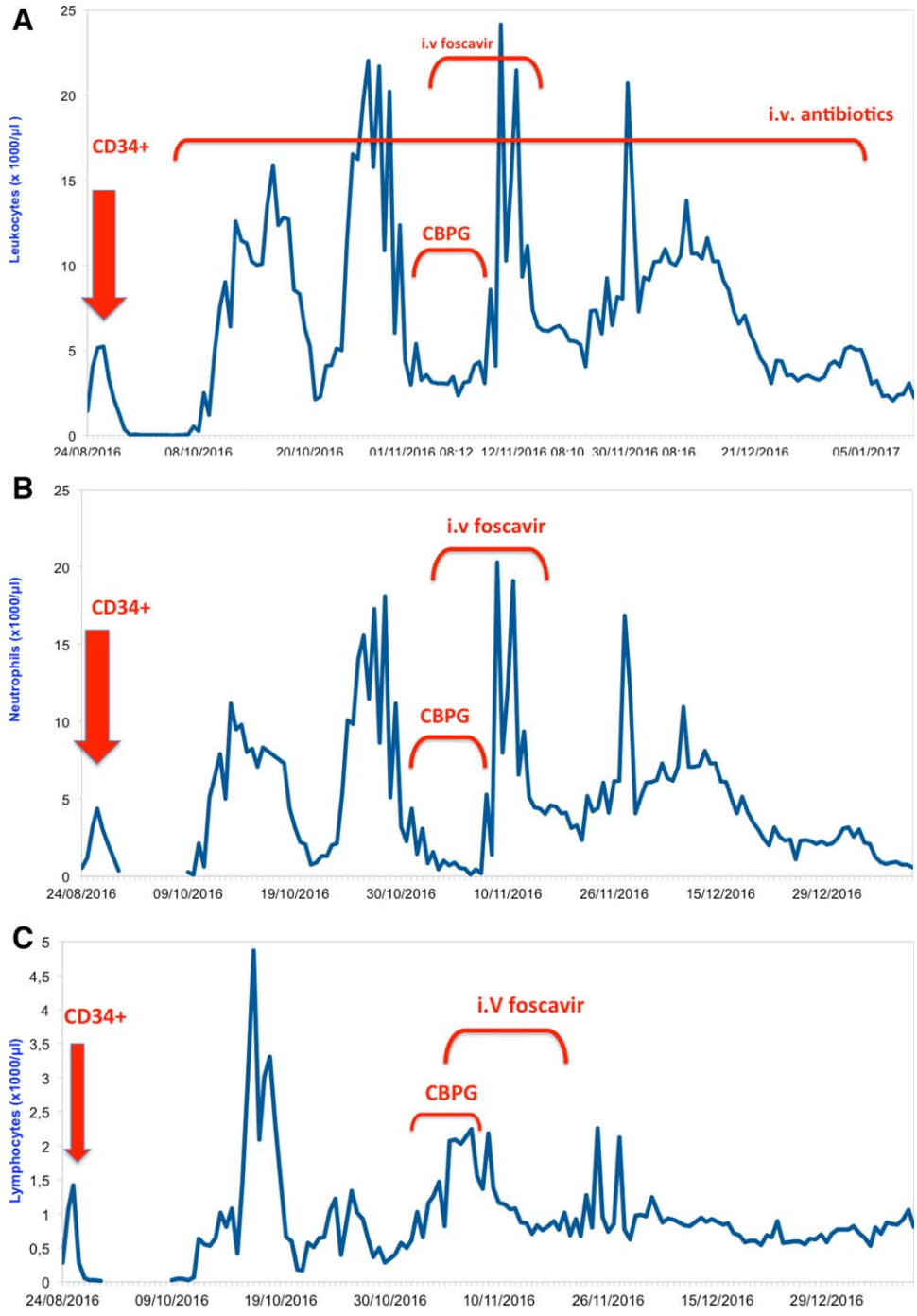

Fig. 2. Trend of total (A) leukocytes, (B) neutrophils, and (C) lymphocytes. After CBPG applications, a marked rise of lymphocytes is observed. [Color figure can be viewed at wileyonlinelibrary.com]

improvement once the oral mucositis was cured. Our findings are also in keeping with similar results obtained by Tadini and colleagues using CBPG for the treatment of dystrophic recessive epidermolysis bullosa.[14,15] Moreover, the trend of lymphocytes showed a peak immediately after CBPG application, which might have helped to clear up the CMV infection. We cannot explain this finding, but we would like to suggest that CBPG application may have triggered this rise in lymphocytes. Nevertheless, the recovery of lymphocyte counts may have occurred independently from the use of CBPG. In this regard, previous studies have shown that platelet factor 4 (PF4) inhibits cytokine release of CD4+/CD25− T cells but up regulates cytokine release of CD4+/CD25+ regulatory T cells.[16] Recently, an abstract publication reported that CD4+ and CD25+ T cells contribute to CMV suppression.[17] It is

important to stress that antiviral CMV therapy (Foscavir) was also started and that the clearance of CMV infection may not necessarily have been related to the use of CBPG.

To the best of our knowledge, this is the first report on the successful use of CBPG for oral mucositis after chemotherapy without any side effects, even after partial deglutition of the gel itself. The positive outcome of our patient supports the need for controlled studies on the efficacy of CBPG for the treatment of severe oral mucositis in patients who receive treatment with high-dose chemotherapy.

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CONFLICT OF INTEREST

PR is cofounder of Episkey S.R.L., an Italian start-up company developing novel reagents and products from cord blood. All other authors have no conflicts of interest to declare.

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