

Successful treatment of massive gastrointestinal hemorrhage in acute biphenotypic leukemia with recombinant factor VIIa (NovoSeven)

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Acute biphenotypic leukemia is a very rare malignancy of childhood. Hemorrhage is a frequent complication of these patients. An 18-year-old-male with acute biphenotypic leukemia developed massive gastrointestinal bleeding that was thought to be due to thrombocytopenia during chemotherapy-induced pancytopenia and did not respond to conventional therapy. Although the prothrombin time and the partial thromboplastin time were within normal limits, inspired by the success in thrombocytopenia and platelet function disorders we decided to use recombinant activated factor VII (rFVIIa) as a last resort. After using a single dose (65 µg/kg) of rFVIIa on the fifth day of bleeding, the bleeding ceased immediately. rFVIIa may be a novel therapeutic alternative in leukemia or chemotherapy-associated massive bleeding. *Blood Coagul*

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Introduction

Leukemias are the primary malignancies of childhood. Acute biphenotypic (hybrid or mixed lineage) leukemia, carrying both myeloid and lymphoid markers, constitutes less than 1% of leukemias [1,2]. In these patients, hemorrhage is a frequent complication of thrombocytopenia, the leukemia itself, cytotoxic drugs such as L-asparaginase, disseminated intravascular coagulation and complicating infections [3,4]. Large volumes of blood product transfusion support are required for the normalization of hemoglobin and coagulation.

Recombinant activated factor VII (rFVIIa) is a novel hemostatic agent recommended in all kinds of bleedings in hemophiliacs with inhibitors [5]. On the other hand, it improves thrombin generation via enhancement of the tissue factor-dependent pathway [6] and has been used for the treatment of thrombocytopenia and platelet function disorders [7–9]. We report successful administration of rFVII in a biphenotypic leukemia with massive gastrointestinal bleeding.

Case report

An 18-year-old, 55 kg male, presented with cough, conjunctival hemorrhage, fatigue and dyspnea. The patient had been examined in another hospital and was referred to us with a presumptive diagnosis of leukemia. He had no personal or family history suggestive of bleeding disorder. Physical examination revealed a

conjunctival hemorrhage, swelling of the face, edema of the feet, disseminated purpuras and bruising, and hepato-splenomegaly (8 cm below the costal margin). The blood pressure was 130/70 mmHg, and the pulse rate was 116/min. Chest X-ray showed enlargement of mediastinal lymph nodes (larger than 3 cm). Cerebrospinal fluid involvement was initially negative. The results of bone marrow aspiration and biopsy material by morphological examination, immunophenotyping and cytogenetics revealed acute biphenotypic leukemia.

Although the patient was initiated on the CCG 1961 high-risk acute lymphoblastic leukemia treatment protocol (Table 1), a remission could not be obtained on day 28. Three days later, on the 34th day of hospitalization, pancytopenia developed, followed by gastrointestinal bleeding that could not be managed with conventional therapy such as single-donor apheresis platelet infusions and fresh frozen plasma replacement. The patient did not receive any growth factors. The day before bleeding the hemoglobin level was 9.4 g/dl, but it fell to 5 g/dl abruptly by hematemesis (approximately 1 l) and melena. This was considered to be a massive gastrointestinal bleed (Table 2). A pediatric surgery consultation suggested endoscopy of the gastrointestinal system but it was postponed due to hemorrhagic diathesis. In the mean time, because of intravenous fluid replacement and continuous blood product infusion, large volumes of blood were needed

Table 1 CCG-1961 high-risk acute lymphoblastic leukemia induction protocol

| Days | Drug | Administration |
|-------------------|--|----------------|
| 0 | Cytosine arabinoside, 70 mg | Intrathecal |
| 7 | Methotrexate, 12 mg | Intrathecal |
| 0, 7, 14, 21 | Vincristine (1.5 mg/m ²), 2 mg | Intravenous |
| 0, 7, 14, 21 | Daunomycin (25 mg/m ²), 40 mg | 2 h infusion |
| 3–21 (nine doses) | L-asparaginase (6000 U/m ²), 10 000U | Intramuscular |
| 0–27 | Dexamethasone (6 mg/m ²), 10 mg | Per-oral |

to be given to the patient, which resulted in widespread edema (including the scrotum and legs) and weight gain of 25 kg. The patient developed mental confusion and the family was anxious. On the fifth day of bleeding, rFVIIa (NovoSeven; Novo Nordisk, Copenhagen, Denmark) in a dose of 65 µg/kg (total 3.6 mg) was added to the treatment (intravenous bolus injection in 5 min). The melena ceased immediately. Although the patient had no bleeding the following day, 1 U packed red cells and 4 U platelets were given to the patient for the normalization of blood values. He did not have any other bleeding afterwards. The clinical status of the patient improved rapidly and he was ready to receive another chemotherapy protocol 4 days later. Then the treatment protocol of CCG 2961 for acute nonlymphoblastic leukemia was initiated (Table 3). A remission could not be sustained after this treatment. The patient developed a pulmonary infection during the pancytopenia period. The treatment failed and he died on day 73 of hospitalization.

Discussion

Acute biphenotypic leukemia is generally resistant to chemotherapy protocols and characterized with bleeding complications [10]. rFVIIa was selected to achieve hemostasis because it provides site-specific thrombin generation by enhancing the tissue factor:FVIIa assembly at the site of vessel injury [11]. It was initially developed for the treatment of bleeding disorders associated with factor VIII and factor IX inhibitors, and has also been used effectively in the management of factor VII deficiencies and platelet function defects [12–15]. But the optimal dose and duration is controversial. It can be used in bleedings that are unresponsive to conventional methods or if there are contraindications to the use of conventional blood product administration. On the other hand, the procoagulant effect of rFVIIa at sites of vascular damage could also contribute to its hemostatic action in platelet disorders. Collagen adherent platelet developed on an early procoagulant surface, as revealed by increased immunocytochemical labeling with annexin V–gold complexes [16].

More recently rFVIIa has been used successfully in the management of intractable intra-abdominal hemorrhage in two patients [17]. Each of the patients had had Crohn disease and intractable intra-abdominal hemorrhage that failed to respond to the conventional therapy. On the other hand, it has been used successfully in a few cases of acute leukemia crisis with massive bleeding due to thrombocytopenia. The first case had a

Table 2 Hematologic parameters and blood components support during gastrointestinal bleeding

| Days* | Hemoglobin (g/dl) | Hematocrit (%) | White blood cells (10 ⁹ /l) | Platelets (10 ⁹ /l) | Prothrombin time (s) | aPTT (s) | Fibrinogen (mg/dl) | FDP | Red cell packed (U) | Platelets (U) | Fresh frozen plasma | rFVIIa (µg/kg) |
|-------|-------------------|----------------|--|--------------------------------|----------------------|----------|--------------------|----------|---------------------|---------------|---------------------|----------------|
| 0 | 9.4 | 29 | 1150 | 52 | 14.7 | 32 | 444 | > 5 < 20 | | | | |
| 1 | 5 | 16 | 980 | 32 | | | | | 1 | 4 | 1 | |
| 2 | 3.9 | 13 | 570 | 61 | | | | | 1 | 8 | – | |
| 3 | 5.2 | 15 | 700 | 60 | | | | | 2 | 4 | – | |
| 4 | 3.9 | 12 | 700 | 44 | | | | | 2 | 8 | 1 | |
| 5 | 6.5 | 19 | 900 | 46 | 11.5 | 30.7 | | | 2 | 8 | 1 | 65 |
| 6 | 7.7 | 23 | 1000 | 45 | | | | | 1 | 4 | – | |
| 7 | 8.4 | 25 | 1500 | 49 | 13.2 | 31.8 | | | – | – | – | |

aPTT, activated partial thromboplastin time; rFVIIa, recombinant activated factor VIIa. *Day 0 is the day before bleeding

Table 3 CCG-2961 IDA.DCTER acute myeloid leukemia induction protocol

| Days | Drug | Administration |
|---------------|--|-------------------------------|
| 0, 14 | Cytosine arabinoside, 70 mg | Intrathecal |
| 0, 1, 2, 3 | Idarubicin (5 mg/m ²), 8 mg | 30 min infusion |
| 0–3 and 10–13 | Cytosine arabinoside (200 mg/m ²), 330 mg | 24 h infusion |
| 0–3 and 10–13 | Etoposide (100 mg/m ²), 165 mg | 24 h infusion |
| 0–3 and 10–13 | 6 Thioguanine (100 mg/m ²), 160 mg | Per orally, twice daily |
| 0–3 and 10–13 | Dexamethasone (6 mg/m ²), 10 mg | Per orally, three times daily |
| 10–13 | Daunomycin (20 mg/m ²), 32 mg | 24 h infusion |
| After 16 | Granulocyte colony-stimulating factor, 5 µg/kg per day | Subcutaneous |

leukemia blast crisis and developed subdural hematoma, and the other case had leukemia and massive hemorrhage from the gastrointestinal tract [18,19]. The first patient was given 11 doses of 100 µg/kg rFVIIa, every 2 h for the first five doses and the following six doses were given at 4 h intervals. The second patient was given one single dose of 90 µg/kg rFVIIa.

Similarly, our patient was given a single dose of rFVIIa for intractable gastrointestinal hemorrhage that had failed to respond to conventional therapy and responded immediately (after first dose) to rFVIIa, after which massive gastrointestinal bleeding ceased, and provided the use of another course of chemotherapy. Since rFVIIa is given at a dose of 70–90 µg/kg in hemophiliacs with inhibitors, we thought that it would be appropriate to use a similar dose in our case. The hematologic and the coagulation parameters (prothrombin time, activated partial thromboplastin time) obtained after 36 h of administration of rFVIIa did not change significantly.

The price of rFVIIa has been a major concern. However, preparation of platelets including the cost of apheresis, disposable sets and irradiation may exceed the cost of rFVIIa when multiple transfusions of platelets need to be given.

We believe that rFVIIa may be an alternative in leukemia or chemotherapy-associated massive bleeding when conventional hemostatic treatment fails. More studies are needed in order to reach a final conclusion on the effects of rFVIIa in bleedings associated with leukemia or chemotherapy-induced thrombocytopenia.

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