Case Report

Successful Control of Massive Bleeding in a Child with Burkitt’s Lymphoma via a Biosimilar Recombinant Activated Factor VII (AryoSeven™)

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We describe a case of a 4-year-old girl with Burkitt’s lymphoma, who suffered from a massive gastrointestinal hemorrhage 3 days after chemotherapy. In spite of applying the common practice in correction of coagulopathy, thrombocytopenia persisted and bleeding became life-threatening. In the present case report, we report a successful control of bleeding with a single-dose administration of a biosimilar recombinant activated human factor VII (AryoSeven).

1. Introduction

Recombinant activated human factor VII (rFVIIa) is a hemostatic agent principally licensed to treat bleeding episodes and perioperative management in hemophilia A or B adults and children with inhibitors and adults with acquired hemophilia, congenital factor VII (FVII) deficiency, and Glanzmann’s thrombasthenia. These indications may be presented only in a small population. rFVIIa has been widely used in off-label indications of managing bleeding episodes. The leading use of off-label indications includes managing patients suffering from coagulopathies, for example, massive, uncontrollable, or sometimes intractable hemorrhage in trauma patients [1].

rFVIIa has been found to enhance the thrombin generation on preactivated platelets. Therefore, it is assumed that the use of rFVIIa can be beneficial in providing hemostasis in other situations characterized by massive bleedings and impaired thrombin generation [2]. AryoSeven is an rFVIIa recently manufactured via recombinant technology in Iran by AryoGen pharmed. It has been proved similar to its originator medicine, NovoSeven® [3].

Notwithstanding the significant increase in pediatric case series, to date the bulk of literature on off-label use of rFVIIa has been confined to adult population. In the current study, we report a Burkitt’s lymphoma case suffering from a massive GI bleeding which was controlled with a single administration of AryoSeven following the unresponsive transfusion of appropriate blood products.

2. Case Report

A 4-year-old girl was referred to our center with presentation of abdominal pain. Diagnostic sonography revealed an intussusception in this patient. Surgery was performed and a large mass was seen in ileocecal area. After the mass biopsy, Burkitt’s lymphoma stage IIb was diagnosed since other organs were not involved.

Chemotherapy was performed in accordance with the intermediate risk group protocol named LMB89. The first course started with one dose of COP (CM 300 mg/m² vincristine 1 mg/m² and 60 mg/m² prednisolone; prednisolone was continued for 7 days). One week later, the second course was administered with COPADMI (CM IV 250 mg/m²/dose, MTX 3000 mg/m², doxorubicin 60 mg/m², Vincristine 2 mg/m², and 60 mg/m² Prednisolone; prednisolone was continued for 5 days). Three days after the second chemotherapy course, the patient experienced febrile...
neutropenia. In spite of appropriate antibiotic therapy cef-
tazidine 800 mg IV, vancomycin 250 mg IV, and flucona-
zole 50 mg were administered with supportive therapy. The
patient deteriorated and suffered from massive lower GI
bleeding. Her blood test is described in Table 1. Since
our patient suffered from Burkitt’s lymphoma, she did not
experience b symptoms.

The patient received several units of pack cell, 0.25 unit/kg
platelets, 15 cc/kg fresh frozen plasma, and some doses of
cryoprecipitate for more than 3 days which is explained in
Table 2. Different abdominopelvic sonographies, which were
complemented with CT scan, showed pancolitis. Treatment
was administrated with octreotide at a dose of 1 μg/kg/h. It
is worth mentioning that octreotide administration in this
situation counts as an off-label indication but, because of its
perfect efficacy at esophageal bleeding, we used it for second-
line therapy, but no clinical response was observed.

After 72 hours of refractory and severe bleeding, the
patient was switched to 90 μg/kg injection of AryoSeven.
Bleeding was successfully controlled 1 hour after administra-
tion of a single dose of AryoSeven. Vital signs were stabilized.
The lowest haemoglobin concentration at the time of blood
haemostasis was 6 g/dL and no more decrease in hemoglobin
concentration was observed. The patient received 10 cc/kg
pack cell (PC) two times as a result of the latest severe
bleeding and low hemoglobin. Patient’s PT, PTT, and INR
are declared in Table 3.

In order to identify the source of bleeding, the patient
underwent endoscopy and colonoscopy after her general
condition was stabilized. No specific finding, except for
a severe mucosal fragility, was found. Her last lab data
are presented in Table 4, 12 hours after administration of
AryoSeven.

Patient’s chemotherapy was continued, her primary dis-
ease was at remission, and there was no sign of GI bleeding
ever since. For other chemotherapy cycles, GCSF administra-
tion was performed to prevent febrile neutropenia. The levels
of fibrinogen were not evaluated during the study because the
required equipment was not available.

3. Discussion

AryoSeven is activated coagulation recombinant factor VII
which is produced by AryoGenPharmed. The biosimilarity of
AryoSeven with NovoSeven has been approved according to
the randomized, multicenter, double-blind clinical trial [4].

The usual dosage for recombinant factor VII injection is 90–120 μg/kg, but it is completely dependent on patient’s clinical
situation. Since the clearance of this medication is higher
in pediatrics, choosing the median dose (90 μg/kg) was
intelligent. Critically ill children with malignancies are prone
to various hard to control situations. Bleeding is one of these
situations that can be in many cases refractory, intractable,
and life-threatening. These situations are important causes
of morbidity and mortality. It is truly critical to perform
the appropriate task to manage hemorrhage in patients with
thrombocytopenia and haematologic malignancies. First-
line strategy should be considered as appropriate blood
transfusion and locating the source of bleeding. Critically ill
patients may be at more risk and even haemodynamically
too unstable to endure surgical or diagnostic procedures. If
platelets and FFP transfusion are not successful in controlling
severe GI bleeding, rFVIIa and octreotide administration
have been shown to be effective alternative treatment options
[5–7].

The mechanism of rFVIIa is generation of thrombin and
platelet, activation of factor X, and formation of haemo-
static plug [8]. There are established dose ranges in labeled
and unlabeled rFVIIa administration. Currently, there is no
universally accepted standard on monitoring the effect of
rFVIIa. European consensus recommends that the efficacy be
monitored visually and according to reductions in transfu-
sion requirement [8]. Apparently, there are increasing calls
for investigations on establishing a reliable and trustworthy
guideline in off-label use of rFVIIa, which can reduce mor-
tality [9].

Lee et al. described 3 cases of pediatric oncology patients
with severe GI bleeding with no sufficient response to blood
transfusions, in which rFVIIa was administered with dose
range of 88–102 mcg/kg/dose. They reported that the use of
rFVIIa resulted in a reduction in blood product support
requirement and administration of rFVIIa was effective in 2
out of 3 patients in stopping the bleeding [5]. Our patient
received octreotide prior to AryoSeven after having no
response to first-line treatment such as platelet and FFP
transfusion. The patient’s response to AryoSeven adminis-
tration was rapid and acceptable. The major bleeding was
successfully stopped and there were no more decrease in
Hb which might be an indicator of possible microvascular
bleeding.

In conclusion, if there is no response to supportive ther-
apy and administration of octreotide in controlling bleeding,
use of recombinant factor VIIa can be lifesaving.

4. Conclusion

According to wide range of off-label indications of recom-
binant factor VIIa, we can say that it could be a wise
option at refractory bleedings as the second-line therapy. The
important problem is dose modification at off-label situations
because there are some reports of thromboembolic events
in off-label indications which were not fatal and not life-
threatening.
Table 2: Different blood product injection and vital sings during 3 days of bleeding.

| Blood product | Unit | Body temperature before injection | Blood pressure before injection | Pulse before injection | Breath before injection |
|---------------|------|----------------------------------|--------------------------------|------------------------|-------------------------|
| PC            | 1 U  | 37                               |                                | 88                     | 22                      |
| Cryoprecipitate|      |                                  |                                |                        |                         |
| FFP           | 170 mL | 37                              |                                | 88                     | 22                      |
| PC            | 4 U  | 38                               | 126/48                         | 124                    | 25                      |
| FFP           | 170 mL | 37.5                             | 140/98                         | 96                     | 32                      |
| PC            | 4 U  | 37                               | 90/50                           | 123                    | 12                      |
| PC            | 3 U  | 37                               | 110/60                          | 110                    | 24                      |
| FFP           | 170 mL | —                                |                                | —                      | —                       |
| PC            | 3 U  | 37                               | 90/50                           | 122                    | 12                      |
| PC            | 3 U  | 38                               | 90/50                           | 120                    | 12                      |
| FFP           | 170 mL | 37.3                             | 90/50                           | 108                    | 30                      |
| PC            | 3 U  | 37                               | 90/50                           | 120                    | 32                      |
| PC            | 3 U  | 37                               | 90/50                           | —                      | —                       |
| FFP           | 200 mL | 37                               | 100/60                          | 134                    | 28                      |

Table 3: Coagulating factor evaluation during bleeding and treatment.

| Date                        | PT patient | PT control | PT activity | INR | PTT |
|-----------------------------|------------|------------|-------------|-----|-----|
| One day before bleeding     | 12         | 12         | 100         | 1   | 31  |
| First day of bleeding       | 12         | 12         | 100         | 1   | 30  |
| Second day of bleeding      | 13.8       | 12         | —           | 1.3 | 28  |
| Third day of bleeding       | 12         | 12         | —           | 1   | 29  |

Table 4: Lab data 12 hours after administration of AryoSeven.

| Lab data                     | 12 hours after AryoSeven™ injection |
|------------------------------|-------------------------------------|
| WBC                          | 3880/mm³                             |
| Hb                           | 11.7 g/dL                            |
| Plt                          | 65000/mm³                            |
| PT                           | 12 seconds                           |
| PTT                          | 34 seconds                           |
| FDP and D-Dimer              | Normal                               |

A randomized clinical trial for off-label indication of recombinant FVIIa in pediatric hemorrhage could be helpful in assessing the safety and efficacy of this medication.

Competing Interests

The authors declared that there are no competing interests.

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