Therapeutic Plasma Exchange in Children with Neutropenic Sepsis: Single Center Experience

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ABSTRACT

Objective: The mortality rate is high for severe sepsis and septic shock. Presently, there are no specific treatments that can reduce mortality in patients with sepsis and multiple organ dysfunction. Therapeutic plasma exchange (TPE) is the automatic separation of a patient's plasma using medical devices and its replacement with healthy donor plasma. TPE may be beneficial in selected cases, even though not routinely recommended by international sepsis guidelines.

Methods: For the present study, file records of three children with neutropenic sepsis who had undergone TPE between March 2015 and June 2016 were retrospectively reviewed.

Results: Two patients with acute leukemia, one patient with stage IV Burkitt lymphoma. All patients showed positive blood cultures. *Candida krusei* with *Klebsiella pneumoniae* was isolated in one patient, *K. pneumoniae* was isolated in the other patient, and *C. krusei* in the last patient. Multiple organ dysfunction developed in all patients and they showed no response to supportive therapy. Plasma exchange was performed 5, 1, and 13 times, respectively. After TPE, two patients fully recovered and one patient died due to natural course of the disease. None of the children developed complications associated with this procedure.

Conclusion: TPE may be considered as an alternative treatment in children with neutropenic sepsis and multiple organ failure who do not respond to conventional sepsis treatment.

Keywords: Neutropenic sepsis, children, therapeutic plasma exchange

INTRODUCTION

Neutropenic fever is a common complication observed in children receiving chemotherapy. It remains to be the major cause of morbidity and mortality despite advances in treatment (1). More than 50% of patients with neutropenic fever develop systemic inflammatory response syndrome, while severe sepsis and septic shock occurs in 20-30% and 5-10%, respectively (1-4). In patients with hematological malignity-related neutropenic fever, mortality rates were 35% for severe sepsis, 47% for septic shock, and up to 85% for multi-organ failure (5).

The conventional treatment for sepsis includes infection source control, intravenous treatment with antibiotics, fluid replacement, inotropic drugs, and supportive therapies such as mechanic ventilation (6). Plasma exchange is a procedure in which a patient's plasma is removed from the whole blood using a medical device and replaced by albumin and/or fresh frozen plasma obtained from healthy donors (7, 8). Particularly, in sepsis accompanied by organ failure, the benefits of therapeutic plasma exchange have been established by the currently growing evidence (1, 9-14). Plasma exchange is used to remove pro-inflammatory mediators; replace immunoglobulins, procoagulant, and natural anti-coagulant proteins; and restore hemostasis (10, 15). Herein, we present our experience with plasma exchange in three pediatric patients who developed neutropenic sepsis and multi-organ failure after chemotherapy.

METHODS

The study included two acute leukemia patients aged 7 and 17 years and one Burkitt's lymphoma patient aged 12 years. The patients developed neutropenic sepsis and multi-organ failure after chemotherapy between 2015 and 2016. Voluntary consent was obtained from the legal guardians of the patients. Patients' medical records were reviewed retrospectively. Physical examination findings, laboratory tests, culture results, vital signs, number of procedures, and time of recovery after the procedure and during neutropenic fever were recorded. Therapeutic plasma exchange was performed on all patients using the Spectra Optia device® and with fresh frozen plasma and albumin.

CASE 1

A 7-year-old male patient with acute lymphoblastic leukemia developed neutropenic fever on Day 56 of chemotherapy. Diffuse oral mucositis was observed. The absolute neutrophil count (ANC) was 0/mm^3. Dual antimicrobial therapy (cefepime and amikacin) was initiated. As the fever persisted, vancomycin was added on the third day of neutropenic fever, and liposomal amphotericin B was added on the sixth day. *Klebsiella pneumoniae* was isolated from the blood cultures obtained during this period. Due to resistance to cefepime, meropenem was used as a replacement, to which the bacteria were susceptible. Erythrocyte, apheresis, and granulocyte suspensions were transfused as

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required based on blood counts and physical examination findings. A blood culture obtained on Day 15 of neutropenic fever was positive for *Candida krusei*. Amphotericin B susceptibility could not be evaluated on the antibiogram test but due to persisting fever, and voriconazole, to which susceptibility was found, was added to the treatment. Hepatosplenomegaly developed (the liver was 34 cm below the costal margin on the midclavicular line, and the spleen was 5-6 cm below the costal margin). Abdominal tomography showed multiple millimetric hypodense nodules in the spleen. Based on these findings, hepatosplenic candidiasis was diagnosed. Circulatory and respiratory failure developed on Day 20 of neutropenic fever. Extremely severe neutropenia persisted (ANC: 0/mm^3). Laboratory results were as follows: erythrocyte sedimentation rate (ESR): 86 mm/h, C-reactive protein (CRP): 26 mg/dL (reference range: 0-0.5), procalcitonin: 18 ng/mL (reference range: 0-0.8), total/direct bilirubin: 2.8/2.1 mg/dL, blood urea nitrogen: 44.5 mg/dL, and creatinine: 1.1 mg/dL. Physical examination findings were respiration rate: 60/min, partial oxygen pressure: 92 mm/Hg, cardiac apex beat: 160/min, and blood pressure: 80/50 mm/Hg. The patient was transferred to the pediatric intensive care unit. Oliguria developed and liver function test values were increased (alanine aminotransferase: 489 U/L, aspartate aminotransferase: 317 U/L). The patient's overall condition gradually deteriorated despite treatment with fluid replacement, diuretics, and inotropic drugs. Since the patient was non-responsive to medical treatment, central venous catheterization was performed on Day 21 of neutropenic fever, and five sessions of plasmapheresis was performed every other day. Procedure-related complications were not observed. Organ failure findings fully recovered by Day 30 of neutropenic fever. Antifungal treatment was continued up to 3 months. Chemotherapy was resumed.

CASE 2

A 17-year-old male patient with Burkitt's leukemia was initiated on cytodestructive chemotherapy. Upon development of tumor lysis syndrome, a central venous catheter was placed and hemodialysis was performed for 3 days. Neutropenic fever developed on Day 6 of chemotherapy. Physical examination revealed diffuse mucositis. Laboratory test results were as follows: ANC: 100/mm^3, ESR: 20 mm/h, CRP 3 mg/dL, and procalcitonin 1.17 ng/mL. Dual antimicrobial therapy (meropenem and amikacin) was initiated. As the fever persisted, vancomycin was added on the third day of neutropenic fever, and liposomal amphotericin B was added on the fifth day. *Klebsiella pneumoniae* was isolated from blood and catheter cultures on Day 7 of neutropenic fever. Due to resistance to meropenem, colistin was initiated to which the bacteria were susceptible. The catheter was removed due to suspected catheter infection. The patient's fever persisted. Repeated blood cultures were also positive for *Klebsiella pneumoniae*. On Day 11 of neutropenic fever, the overall status further deteriorated, and abdominal distention developed. On physical examination, the sclerae were icteric, abdominal distention was observed (the liver was palpable at 5-6 cm below the costal margin on the midclavicular line, and the spleen was palpable at 4-5 cm below the costal margin on the midclavicular line); bilateral wheezing and prolonged expirium were found on lung auscultation. The patient was transferred to the pediatric intensive care unit. Physical examination findings were as follows: temperature: 38.8°C, respiration rate: 26/min, cardiac apex beat: 153/min, blood pressure: 90/60 mm/Hg, and partial oxygen pressure: 90 mm/hg. Laboratory test results were as follows: ANC: 100/mm^3, ESR: 58 mm/h, CRP: 31 mg/dL, procalcitonin 7.4 ng/mL, blood urea nitrogen: 25 mg/dL, creatinine: 1.27 mg/dL, and total/direct bilirubin: 42./4 mg/dL. Erythrocyte suspension, apheresis, and granulocyte suspension were transfused. Nasal positive pressure ventilation and intense inotropic supportive treatment were applied. One session of plasma exchange was performed on Day 12 of neutropenic fever. The procedure was successful without any complications. The following day, respiratory failure developed and the patient required intubation. The patient remained hypotensive despite intense inotropic support, and he died on Day 14 of neutropenic fever.

CASE 3

A 12-year-old male patient diagnosed with Stage IV Burkitt's lymphoma developed neutropenic fever on Day 6 of chemotherapy. On physical examination, the abdomen was distended and diffuse ascites was present. The ANC was 200/mm^3. Dual antimicrobial therapy (meropenem and amikacin) was initiated. As the fever persisted, vancomycin was initiated on the third day of neutropenic fever, and voriconazole was initiated on the sixth day. On Day 11 of neutropenic fever, metabolic acidosis, respiratory distress, circulatory dysfunction and hypotension developed. The patient was transferred to the pediatric intensive care unit. The ANC was 0/mm^3. Physical examination findings were as follows: respiration rate: 50/min, partial oxygen pressure: 92 mm/Hg, cardiac apex beat: 140/min, and blood pressure: 80/50 mm/Hg. The patient was operated for intestinal perforation and colostomy was performed. Nasal oxygen, fluid replacement, and inotropic supportive treatments were provided. A lung X-ray showed bilateral pulmonary consolidations at basal segments. Erythrocyte, platelet, and granulocyte suspensions were transfused as required based on blood counts and physical examination findings. The patient's body temperature was not under control, and he was intubated and put on ventilator on Day 15 of neutropenic fever due to respiratory failure. *Candida krusei* was isolated in a blood culture. Generalized edema, oliguria, and direct hyperbilirubinemia developed. Laboratory findings were as follows: ANC: 0/mm^3, ESR: 57 mm/h, CRP: 19 mg/dL, procalcitonin: 32 ng/mL, total/direct bilirubin: 3.9/3.1 mg/dL, blood urea nitrogen: 49.7 mg/ dL, and creatinine: 1.2 mg/dL. Fluid replacement and diuretic treatment was given. Oliguria and edema persisted. Central venous catheterization was performed on Day 16 of neutropenic fever, and a total of 13 plasma exchange sessions, daily sessions in the first week and every other day the following week, were performed. No procedure-related complications were observed. Renal functions had recovered, edema had remitted, and bilirubin levels were restored to normal (total bilirubin/direct bilirubin: 0.5/0.22 mg/dL). The respiratory pattern returned to normal and he was extubated. He was transferred back to the clinic on Month 1 of neutropenic fever and chemotherapy was resumed.

DISCUSSION

Neutropenic fever is the most common and serious complication of chemotherapy in children with malignancies. The rate of neu-

tropenia following chemotherapy is 5-10% in patients with solid tumors, more than 20% in children with hematological malignancies, and up to 70-100% in patients who undergo bone marrow transplantation (16). In neutropenic patients with sepsis, the major prognostic factors include prolonged neutropenia (ANC of <500/mm^3 more than 10 days); delayed antimicrobial treatment; remission status of the underlying malignancy; time to admission to intensive care; presence of invasive aspergillosis; presence of neurological, hepatic, or respiratory insufficiency; and requirement for vasopressor treatment (1, 17). Our cases had negative prognostic risk factors, such as prolonged neutropenia, respiratory failure, and requirement for vasopressor treatment. In case of multi-organ failure in patients with malignancy-related neutropenic fever, the mortality rate is increased up to 85% (16). In our cases, multi-organ failure was observed and the one patient died.

In sepsis, cytokine, chemokine, and other pro-inflammatory mediators are released by polymorphonuclear leucocytes and macrophages as a result of exposure to exogenous microbial agents. Occasionally, this inflammatory process essential for host defense can become an inflammatory response that causes damage to the host, and patients can be lost despite appropriate antimicrobial and hemodynamic treatment (14). Currently, mortality and morbidity rates of sepsis and multi-organ failure remain high despite improvements in monitoring and treatment of such cases (1, 9, 14). The interventions and treatment provided for sepsis are suggested to reduce mortality (1). However, unfortunately, our knowledge about management of sepsis in neutropenic patients is limited.

Therapeutic plasma exchange can be used to remove multiple circulating toxic mediators, including endotoxins, pro-inflammatory cytokines, and procoagulant factors, present in patients with sepsis (10, 14). In animals with *Escherichia coli* endotoxin-induced sepsis, increased adhesion molecules, oxidative stress, cytokine concentrations, and granulocyte accumulation in the lung tissue were reported, and reduced oxidative stress and pulmonary granulocyte accumulation was shown following plasma exchange (18). In another study, dead leucocyte levels in blood samples from patients with sepsis was found significantly higher compared to both normal physiological levels and to those from patients without systemic inflammation features; also, dead leucocyte levels in blood were positively correlated with organ dysfunctions (19). Plasma filtration used for patients with sepsis was suggested to significantly reduce blood dead leucocyte concentrations and prevent organ failure through this mechanism (19).

There are few randomized controlled studies in literature about the efficacy of therapeutic plasma exchange in sepsis. Busund et al. (12) reported that the 28-day mortality rates in adult patients were 33% in therapeutic plasma exchange group and 53.8% in the control group; although the difference was significant, the significance value was lower after logistic regression analysis, and there was no significant effect on mortality. In their study including 10 pediatric patients with culture-positive sepsis, thrombocytopenia and multi-organ failure, Nguyen et al. (13) showed that the organ damage score was reduced and that the 28-day survival rate was improved in the group that underwent therapeutic plasma exchange. In a study conducted in Turkey on pediatric sepsis patients with multi-organ failure and thrombocytopenia, mortality rates were significantly lower in the group that was treated with therapeutic plasma exchange compared to the group that was not (20). In a study conducted in 14 pediatric patients, Kawai et al. (11) showed that in children with sepsis-related multi-organ failure, early initiation of therapeutic plasma exchange provided better improvement in organ dysfunctions and less requirement for inotropic agents compared to those with delayed initiation.

The three patients we report here had at least three organ failures. They were non-responsive to intravenous fluid replacement, antimicrobial and inotropic supportive treatments. Therefore, therapeutic plasma exchange was performed to remove circulating cytotoxic substances. Case 1 received 5 sessions of plasma exchange, while Case 2 received 13 sessions, and Case 3 had only 1 session. In the two patients who survived, therapeutic plasma exchange was continued until supportive inotropic treatment was no longer required. There are no established criteria regarding the number and frequency of plasma exchange procedures. However, the general approach suggests that the decision is based on the patient's organ failure criteria. However, determining the time for plasma exchange also remains unclear. Our patients with fungemia showed better response to plasma exchange. The patient with bacterial sepsis showed a very rapidly declining clinical course compared to the other cases and he died. An earlier initiation of the procedure may be life-saving for patients with bacterial sepsis. Further studies are required to eliminate these questions.

In clinical conditions with high mortality risk, there is no absolute contraindication for plasma exchange. The procedure can be performed with adequate inotropic agents and respiration support (11). Potential adverse effects, including urticarial reactions, citrate-related hypocalcemia, catheter-related thrombosis, hemorrhage, infection, and transfusion-related lung injury, should also be considered (21). In our patients, none of the above-mentioned complications developed.

CONCLUSION

In pediatric patients with hematologic malignancies who develop neutropenic sepsis and multi-organ failure and are non-responsive to treatment, therapeutic plasma exchange can be performed in intensive care conditions based on the patient's clinical features and laboratory parameters.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Eskişehir Osmangazi University School of Medicine.

Informed Consent: Verbal informed consent was obtained from the parents of the patients who participated in this study.

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