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Extracorporeal Membrane Oxygenation in the Treatment of acute Monoblastic Leukemia Onset: Setbacks and Imposed Ethical Dilemmas in Developing Countries - Case Report

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ABSTRACT

Background: *The implementation of extracorporeal membrane oxygenation (ECMO) in patients with hematologic malignancies suffering from severe acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF) remains controversial.*

Case presentation: *We present a case of a patient with acute monoblastic leukemia who exhibited rapid-onset MOF. Hemodynamic stability was achieved primarily with pharmacologic vasopressor therapy, followed by mechanical circulatory support via ECMO, in conjunction with a prompt chemotherapy session. The patient had evidence of disseminated intravascular coagulation (DIC) and deteriorating status, characterized by dilated and nonreactive pupils due to multiple hemorrhagic lesions and diffuse brain edema, resulting in a fatal outcome.*

Conclusion: *This case discusses the challenging decision-making process encountered by physicians in the intensive care unit, particularly with the withdrawal or withholding of treatment at the end of life within our legal framework. Current Croatian legislation remains inflexible and fails to correspond with developments in clinical practice and judgments regarding palliative care patients. To provide high-quality treatment to palliative and end-of-life patients, regulatory frameworks and regulations must create a secure environment for both healthcare providers and patients.*

Keywords

Decision-making, End-of-life issues, Futility, Bioethics.

Abbreviations

AMoL: Acute monoblastic leukemia; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive Care Unit; MOF: Multiorgan failure.

Introduction

Acute monoblastic leukemia (AMoL) is a subtype of acute myeloid leukemia characterized by abnormal proliferation of immature monoblasts in the bone marrow and blood. The annual incidence in children and adolescents is 1:100,000. The clinical presentation arises from anemia, thrombocytopenia, and organ infiltration by leukemic cells [1]. The clinical presentation might range from asymptomatic to rapid and severe multiorgan failure (MOF). Currently, the implementation of extracorporeal membrane oxygenation (ECMO) in patients with hematologic malignancies experiencing severe acute respiratory distress syndrome (ARDS) and MOF remains controversial [2].

This case aims to illustrate a rare instance of severe manifestations and complications of AMoL and to examine the challenging decision-making process encountered by clinical practitioners in Intensive Care Units (ICU), particularly with the withdrawal of care under our legal framework.

Case Presentation

A 21-year-old male was admitted to the ICU following diagnostic evaluation and initial resuscitation in the emergency department, where he was initially assessed for suspected splenic rupture. Few days prior, the patient was suspected of having infectious mononucleosis and was discharged to home care with symptomatic therapy. The patient was fully conscious, exhibiting subfebrile temperature, hypotension, sinus tachycardia, tachypnea, and oligoanuria. Initial examination revealed hepatosplenomegalia, pericardial effusions, acute kidney injury, leukocytosis and significantly elevated procalcitonin (PCT) and NT-proBNP.

Upon admission to the ICU, volume optimization with crystalloids, as well as dual vasoconstrictor support using noradrenaline and vasopressin, was initiated. Additionally, empirical antimicrobial and corticosteroid therapy were introduced. The blood count revealed anemia, thrombocytopenia, and leukocytosis, characterized by a predominant monocyte profile. A bone marrow puncture was conducted in consultation with a hematologist to verify the possibility of hematologic malignancy. Subsequent bone marrow examination revealed 95% abnormal blast cells, which, following immunofluorescent characterization, were identified as acute monoblastic leukemia.

The patient's condition rapidly worsened as a systemic inflammatory response developed. Mechanical ventilation with ultraprotective settings was introduced. An urgent MSCT of the thorax revealed extensive bilateral atelectasis affecting involving nearly the entire lower lung lobes. Due to further hemodynamic deterioration, a temporary mechanical circulatory support with veno-arterial ECMO (VA-ECMO) system commenced. Furthermore, an infusion of angiotensin II was started in addition to already introduced noradrenaline and vasopressin. A prompt chemotherapy session utilizing vincristine commenced within 24 hours, accompanied by rasburicase to prevent tumor lysis syndrome. Nevertheless, the patient exhibited indications of disseminated intravascular coagulation (DIC), despite daily intensive management of anemia, thrombocytopenia, and coagulopathy.

On the third day of treatment, atrial fibrillation with 170 bpm occurred, which further aggravated hemodynamic instability. In attempt to stabilize the patient, synchronized cardioversion was performed, but lacked the desired outcome. Consequently, amiodarone and beta blockers were incorporated into the therapeutic regimen. On the same day, dilated and nonreactive pupils were noted, prompting an immediate MSCT of the brain, which revealed bilateral numerous foci of bleeding and diffuse cerebral edema. To manage cerebral edema and decrease intracranial pressure, intensive anti-edematous treatment with osmotherapeutics and hyperventilation was initiated, as surgical decompression was not indicated.

Meanwhile, the disease was verified as AMoL. This type of leukemia is associated with a high incidence of organomegaly, lymphadenopathy, and other tissue infiltration [3]. Also, central nervous system involvement is more common than in most other forms of acute myeloid leukemia, and DIC may be observed in some cases [4], which makes this kind of leukemia progressive in onset and possibly detrimental in outcome.

The hematologist aimed to persist with cytoreductive therapy to diminish systemic proliferation caused by leukemia, so preventing infiltration into brain tissue. Consequently, the chemotherapeutic agent cytarabine was incorporated into the treatment regimen.

On the eighth day, a control MSCT of the brain was conducted, revealing continuing progression of cerebral edema with impending herniation, despite anti-edematous and antiproliferative treatment. Cardiac arrest occurred due to the advancement of the underlying disease and its complications, resulting in the patient's death on the tenth day of intensive care treatment.

Discussion

We here present a case of a young man with a rapid onset and progression of AMoL, accompanied by hemodynamic instability and MOF that required VA-ECMO support. Complications arose during the cytoreductive treatment, specifically a cerebral hemorrhage and harmful cerebral edema, raising questions about the diagnosis of brain death. The already controversial ECMO treatment faced additional ethical questions that required prompt resolution in a stressful environment.

Is it appropriate to commence ECMO support for a patient with acute leukemia?

The decision was reached by the assembly of anesthesiologists, intensivists and hematologists, grounded in clinical experience and research findings. Despite the absence of randomized controlled trials in this area, a substantial global case series indicated a potential favourable outcome [5]. The overall prognosis of hematologic malignancies has improved due to novel chemotherapeutic protocols, stem cell transplantation, and enhanced supportive care. Currently, the implementation of ECMO in patients with hematologic malignancies experiencing severe ARDS remains controversial. However, salvage ECMO support is a viable option for managing moderate to severe ARDS and/or heart failure in pediatric patients receiving chemotherapy or undergoing hematopoietic stem cell transplantation [6,7].

How to determine brain death in patients on ECMO support?

Given the presence of intracranial hemorrhage and edema, along with dilated nonreactive pupils, an issue emerged regarding the appropriate timing to commence brain death determination. Death by neurologic criteria is a permanent state of catastrophic brain injury, very well defined by current guidelines [8]. The

diagnosis necessitates the fulfillment of three criteria: persistent coma, absence of brainstem reflexes, and an inability to breathe autonomously, evaluated through an apnea test. The fundamental objective of the apnea test is to induce hypercapnia to a sufficiently elevated threshold to activate the respiratory drive. The primary challenge in inducing hypercapnia during ECMO support is maintaining hemodynamic stability while ensuring normal oxygenation throughout the procedure. This contributes to the high failure rate and associated hemodynamic complications [9]. Nonetheless, it is crucial to note that there is currently no consensus in guidelines concerning brain death assessment in ECMO. However, ancillary testing, such as examinations of cerebral blood flow or bioelectrical activity, is essential for the confirmation of brain death in patients receiving ECMO support [10].

Decisions Regarding the Discontinuation of ECMO support

Indications for ECMO initiation may be classified as bridge to transplant, bridge to mechanical circulatory support, bridge to recovery, or bridge to decision in patients whose prognoses are uncertain [11]. In our patient ECMO was started as a necessity for hemodynamic stability optimization in vague circumstances, prior to the confirmation of acute leukemia. It is important to note that the prognosis of the illness was uncertain, and the probability of recovery could not be established at the commencement of ECMO support; therefore, we defined ECMO as a bridge to diagnosis.

In the face of incurable illness aggressive ICU care can prolong suffering and may not serve the patient's best interests. Consequently, limitation of life-sustaining treatment, including the withholding or withdrawing of care, has become prevalent in numerous countries. Withdrawal is an active process that typically necessitates a written order and justification, making it likely to be documented. Withholding implies the lack of action and may not necessitate an order. Prior studies identified high variability in prevalence of withdrawal of life-sustaining treatment in the ICU, occurring at many levels: among regions (influenced by regional and religious factors), among specific ICUs, and even among individual intensivists [12].

There are some cultural barriers regarding withdrawal of care, with Croatia as a prominent example. Croatia is classified as an upper-middle-income country located in Southeast Europe. Croatia's universal healthcare system, founded on the values of solidarity and reciprocity, requires public insurance for all people, enabling contributions based on financial capacity while providing basic healthcare services customized to individual requirements. Accordingly, the healthcare system is fairly accessible and rather well-developed. However, the current legal framework's rigidity restricts end-of-life decisions and insufficiently integrates palliative care.

Cultural barriers include confusing the withdrawal of care with the acceleration of death, and certain healthcare professionals may be uncomfortable accepting such treatment options based on their own conception of quality of life, which may differ from that of the patient. This places ICU medical professionals in an challenging position as they balance between patients' wishes, best medical practices, legal obligations, and their own moral principles. A research among medical experts in the Republic of Croatia revealed that life-sustaining treatments were infrequently delivered to end-of-life patients in ICUs. Inotropes and antibiotics were discontinued more frequently than mechanical ventilation. Decisions were primarily made by physicians and rarely by nurses. In over fifty percent of the cases, family members participated in the decision-making process. The findings indicated a predominance of paternalistic and conservative attitudes, consistent with observations in other Southern European countries [13,14].

Given the gravity and urgency of clinical situations in which ECMO is used, consent is often implied but rarely explicitly sought from the patient before initiation. Thus, giving rise to physicians concern about the legality and ethics of withdrawing the therapy. In our legislation, consent is provided by a legal representative for patients lacking the legal capacity to give consent, except in cases of urgent medical intervention. Euthanasia and physician-assisted suicide are illegal and classified as criminal offenses under the criminal code. Likewise, no forms of anticipatory decision-making (i.e., living wills, do-not-resuscitate orders) by patients are regulated by law.

In 2021, the Croatian Ministry of Health published the Guidelines for Quality Improvement of Palliative Care in ICUs [15]. These guidelines indicate that in end-of-life patients, all futile treatment should be limited and that personalized palliative care should be provided.

Palliative care focuses on symptom management, psychosocial and religious support, and plans for future care around those factors. These issues are of extreme importance, particularly for patients with no potential for recovery or transplantation. Palliative care should begin early (when the situation is recognized) and be responsive to acute changes in the patient's health state.

In Croatia, there is still a minority of patients requiring ECMO support as a bridge to decision-making. Due to the development of medical equipment and medical services in tertiary institutions, this number may increase in years to come. This may challenge ethical considerations regarding ECMO continuation for capacitated patients, as the ECMO may turn out to be a "bridge to nowhere". In the case of this young man, ECMO literally became a "palliative bridge to death", where the goal of care was no longer to extend life. Instead, the goal of ECMO support in this situation was to sustain a dignified extent of life and possibly to prepare the patient's family for the inevitable end of life, which they found extremely precious. Due to insufficiently defined legally permitted palliative procedures, attending physicians decided to proceed with withholding and not with the withdrawal of care, which was deemed the more prudent solution.

As we can see, the field of palliative medicine is developing

rapidly, unlike legislation. We have not even managed to solve the basic settings yet, and a new chapter entitled “ECMO as a palliative bridge to death” is already imposing itself on us. All of the aforementioned significantly complicates everyday practice in the ICU since most frequent ethical dilemmas are connected to the patients' uncertain or impaired decision-making capacity and withdrawal or withholding of treatment at the end of life. The reasons for this situation are usually the lack of working protocols, algorithms, and guidelines to assist physicians in decision-making, as well as the lack of experienced ethics services that would help ICU staff make decisions about potential cases of medical futility.

Conclusion

Currently, we are facing a transitional moment as we struggle to integrate palliative care in the ICU in a way that is both effective and legally defined. The initial advancement was the publication of guidelines offering instructions and systematic support for medical practitioners confronting difficult circumstances. However, an additional measure should involve the creation of a Croatian legal framework, since the existing legislation remains inflexible and fails to correspond with developments in clinical practice and judgments regarding palliative care patients. To provide high-quality treatment to palliative and end-of-life patients, regulatory frameworks and regulations must create a secure environment for both healthcare providers and patients.

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