Final degree project

EASIX AS A PREDICTOR OF SEVERE INFECTIOUS COMPLICATIONS IN AML PATIENTS THAT UNDERGO INTENSIVE CHEMOTHERAPY

A Prospective Multicenter Cohort Study

Author: Nisrine Laare el Morabit

Clinical tutor: Dra. Rosa Coll Jordà

Methodological tutor: Dr. Rafael Ramos Santiago

Faculty of Medicine, University of Girona

January 2024

I want to thank to Dr Rosa Coll Jordà, for all the support and the encouragement that she gave during all the process, especially in my lowest moments. I am very grateful to have had you as my tutor.

I also want to thank to the hematology unit of Josep Trueta Hospital, especially, Dr. Jordi Vila and Dra. Marta Sitges and Dr. Nil Albiol, for the good reception while I was on placement.

To Dr. Rafael Ramos and Dra. Ruth Martí for helping me with the methodology and for all the advice they gave me.

I want to thank my parents, for bearing with me and helping me get through all those tough years of university, and my family for their supplications.

Thank you to all my friends that supported and trusted me, you know who are.

And that each person will only have what they endeavored towards 

-Quran 53:39-

Abstract

BACKGROUND: Infections are the most frequent complication and the first cause of mortality in AML intensive chemotherapy. Even though patients are closely monitored and treated for their infections, infection-related mortality is still significant.

The Endothelial Activation and Stress Index (EASIX) score (LDH × creatinine / platelet count) was first developed to predict overall survival in complications related to allogenic hematopoietic transplants. Since then, several studies assessed the EASIX score prediction ability in different diseases, such as, ICANS and CRS in CAR-T therapy, Multiple Myeloma, diffuse large B-cell Lymphoma, COVID-19, sepsis, etc.

To this date, there is no evidence in the current literature of any study that has evaluated the EASIX score in severe infections in newly diagnosed AML patients that undergo intensive chemotherapy.

OBJECTIVES: Main objective is to analyze if EASIX is a predictor of severe infectious complications in newly diagnosed AML patients that undergo intensive chemotherapy. Secondary objectives are to determine whether EASIX associates with treatment related mortality in 28 days, CR and/or CRI.

DESIGN AND METHODS: A prospective-multicenter cohort study will be conducted within the CETLAM group. Each hospital will have a hematologist that will participate in patient recruitment, data collection and database input. Descriptive, bivariate and multivariate analysis are performed.

PARTICIPANTS: Patients with newly diagnosed of AML that have not started treatment yet.

KEY WORDS: *EASIX, acute myeloid leukemia, intensive chemotherapy, severe infections, endothelial dysfunction.*

Index

1. Acronyms and abbreviations

Allo-HCT: Allogenic hematopoietic cell transplantation.

AML: Acute Myeloid Leukemia.

ANC: Absolute neutrophil count.

APACHE-II: Acute Physiology and Chronic Health Evaluation II.

APL: Acute promyelocytic leukemia.

AUC: Arean Under the Curve.

BHV: B Hepatitis Virus.

BSI: Blood Stream Infection.

C: Collaborators.

CAR-T: Chimeric antigen receptor T-cell.

CD: Cluster of differentiation.

CETLAM: Grupo Cooperativo de Estudio y Tratamiento de las Leucemias Agudas y Mielodisplásicas.

CHV: C Hepatitis Virus.

CNS: Central nervous system.

CR: Complete response.

CRI: Complete response with incomplete hematological recovery.

CRL: Cephalocaudal liquid.

CRP: C reactive protein.

CRS: Cytokine release syndrome.

CT: Computed tomography.

CTCAE: Common Terminology Criteria for Adverse Events.

CVC: Central venous catheter.

DAMPs: Endogenous damage-associated molecular patterns.

DCLO: Diffusing Capacity of the Lungs for Carbon Monoxide.

DTP: Differential time to positivity.

EASIX: Endothelial activation and stress index.

EC: Endothelial Cells.

ECOG: Eastern Cooperative Oncology Group performance status.

ET: Endothelin.

GCS: Glasgow Coma Scale.

GVHD: Graft versus host disease.

HIV: Human Immunodeficiency Virus.

HPT: Hematopoietic transplant.

HR: Hazard ratio.

HT: Hematology Team.

ICAM: Intercellular adhesion molecule.

ICANS: Immune effector cell-associated neurotoxicity syndrome.

IL: Interleukin.

INR: Internacional normalized ratio.

LFA-1: Lymphocyte Function-associated Antigen 1.

LPS: Lipopolysaccharide.

MAC: Myeloablative conditioning.

MAP: Mean arterial pressure.

MDS: Myelodysplastic syndrome.

MPD: Myeloproliferative disorders.

MODS: Multi Organ Dysfunction Syndrome.

NO: Nitric Oxide.

PAMPs: Pathogen-associated molecular patterns.

PCT: Procalcitonin.

PI: Principal Investigator.

Plg: Plasminogen.

RIC: Reduced intensity conditioning will ablate completely.

ROS: Reactive oxygen species.

ROC: Receiver Operating Characteristic.

RT: Research Team.

scu-PA: Single chain urokinase-type plasminogen activator.

SOFA: Sequential Organ Failure Assessment.

SPSS: Statistical Package for the Social Science.

S: Student.

ST: Statistician.

SI: Sub investigator.

TFPI: Tissue factor pathway inhibitor.

TLR: Toll like receptor.

TNF-α: Alfa tumoral necrosis factor.

t-PA: Tissue-type plasminogen activator.

TTPa: Activated partial thromboplastin time.

u-PA: Urokinase-type plasminogen activator.

UTI: Urinary tract Infection.

VCAM: Vascular cell adhesion molecule.

VEGF: Vascular Growth Factor.

FEV1: Forced Expiratory Volume.

VLA-4: Very Late Antigen 4.

VRE: Vancomycin-resistant *Enterococcus*.

WBC: White Blood Cell.

WHO: World health organization.

2. Figures and tables

3. Introduction

3.1 Acute Myeloid Leukemia

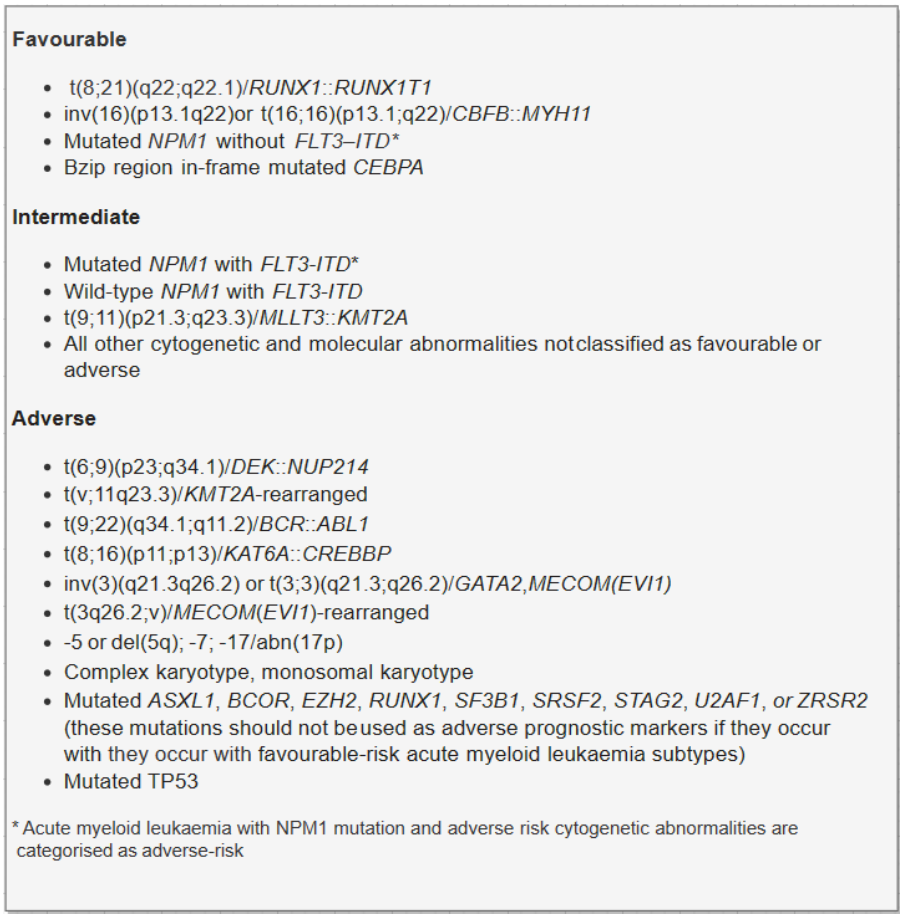
Acute myeloid leukemia (AML) is a bone marrow stem cell cancer characterized by an uncontrolled clonal proliferation and expansion of immature myeloid blasts in the bone marrow and peripheral blood, with a blockage in differentiation and diminished apoptosis, leading to impaired, resulting in thrombocytopenia, anemia, and immunodeficiency (1,2).

AML is most frequent acute leukemia in adults, with an incidence of 3-5/100000 cases annually. It is more common in older adults: two-third are diagnosed around 65 years old (1).

AML is characterized by a series of mutations of the genes involved in hematopoiesis. In most cases, AML appears as *de novo* in a previously healthy person. The exact cause of genetic mutations remains unclear, but some risk factors are previous exposure to ionizing radiation, chemotherapeutic agents, benzene, and smoking; evolution from myeloproliferative disorders (MPD), myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria, and aplastic anemia; and congenital disorders (Down and Fanconi syndrome) (2,3).

AML symptoms appear due to a reduction in all hematopoietic-derived cells. Anemia, weakness, fatigue, dizziness, dyspnea, recurrent infections, excessive bleeding, headaches, bone pain, fever, easy bruising, etc. The physical examination can show pallor, hematomas, hepatomegaly, splenomegaly, rarely lymphadenopathy and in some cases a skin rash due to cutaneous infiltration (1).

The diagnostic evaluation may include complete hemogram and peripheral blood smear, bone marrow aspiration and/or biopsy, bone marrow cytogenetic and molecular study, and blasts immunophenotype to confirm and categorize AML according to a favorable, intermediate or adverse risk (***ELN 2022***) (1).



Favourable

- t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
- inv(16)(p13.1q22)or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
- Mutated *NPM1* without *FLT3–ITD**
- Bzip region in-frame mutated *CEBPA*

Intermediate

- Mutated *NPM1* with *FLT3-ITD**
- Wild-type *NPM1* with *FLT3-ITD*
- t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
- All other cytogenetic and molecular abnormalities notclassified as favourable or adverse

Adverse

- t(6;9)(p23;q34.1)/*DEK*::*NUP214*
- t(v;11q23.3)/*KMT2A*-rearranged
- t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
- t(8;16)(p11;p13)/*KAT6A*::*CREBBP*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*,*MECOM(EVI1)*
- t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged
- -5 or del(5q); -7; -17/abn(17p)
- Complex karyotype, monosomal karyotype
- Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2* (these mutations should not beused as adverse prognostic markers if they occur with they occur with favourable-risk acute myeloid leukaemia subtypes)
- Mutated TP53

* Acute myeloid leukaemia with NPM1 mutation and adverse risk cytogenetic abnormalities are categorised as adverse-risk

Figure 1. *European Leukemia Net 2022 risk categorization. Adapted from (3).*

According to the latest WHO 2022 AML classification, AML diagnosis will no longer be defined by blast cutoff (≥20% in ether bone marrow or peripheral blood), but genetic abnormalities. Now, AML is only defined by the genetic and/or molecular abnormalities and morphology, except in AML with *BCR:ABL1* and AML with *CEBPA*, that still require the 20% blasts cutoff (***Table 1***).

AML treatment generally consists of a two-phase intensive chemotherapy, aiming to control and eradicate, if possible, the disease. The first phase is the induction therapy to complete remission, based on a combination of an anthracycline and cytarabine, followed by the second phase with consolidation therapy based on intermediate to high doses of cytarabine. Some patients may undergo allogenic hematopoietic stem cell transplant after complete remission in induction therapy to completely cure the disease, depending on the patient's risk of relapse (1,4).

Table 1. AML classification (WHO 2022). *Adapted from (5).*

Acute myeloid leukemia with defining genetic abnormalities
Acute promyelocytic leukemia with *PML:RARA* fusion
Acute myeloid leukemia with *RUNX1*:*RUNX1T1* fusion
Acute myeloid leukemia with *CBFB*:*MYH11* fusion
Acute myeloid leukemia with *DEK*:*NUP214* fusion
Acute myeloid leukemia with *RBM15*:*MRTFA* fusion
Acute myeloid leukemia with *BCR*:*ABL1* fusion
Acute myeloid leukemia with *KMT2A* rearrangement
Acute myeloid leukemia with *MECOM* rearrangement
Acute myeloid leukemia with *NUP98* rearrangement
Acute myeloid leukemia with *NPM1* mutation
Acute myeloid leukemia with *CEBPA* mutation
Acute myeloid leukemia, myelodysplasia-related
Acute myeloid leukemia with other defined genetic alterations
Acute myeloid leukemia, defined by differentiation
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute basophilic leukemia
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia

3.1.1 Complications post-induction therapy

AML treatment complications occur due to prolonged pancytopenia. The most common complications are associated with neutropenia and thrombocytopenia, such as, culture negative neutropenic fever or organ hemorrhages (***Table 2***) (6). There are also other complications, which are not related to the treatment, that can be life-threatening, such as leukostasis, tumor lysis syndrome and disseminated intravascular coagulation (4).

Table 2. Complications post-induction chemotherapy in AML. *Obtained from (6).*

Neutropenic complications	Thrombocytopenic complications
Culture negative neutropenic fever	Gastrointestinal hemorrhage
Bacteremia	Retinal hemorrhage
Typhlitis	CNS hemorrhage
Pneumonia	Epistaxis
Fungemia	Gynecologic hemorrhage
Cholecystitis	Hematuria
Appendicitis	
Viral infection	
VRE UTI	

Infection

Patients with AML are at increased risk of life-threatening infections, especially bloodstream infection (BSI), due to intensive and long-lasting chemotherapy-induced neutropenia.

According to several studies, infections are the most frequent complications when undergoing induction therapy, with an incidence of 95% of AML patients that had at least one episode of febrile neutropenia and/or documented (clinically or microbiologically) infection (7–9). These complications are associated with increased morbidity, mortality, and treatment costs (7,10–12). Because of a blunted inflammatory response, infection can be difficult to diagnose and rapidly evolve to sepsis shock, and ultimately multiple organ dysfunction, leading to death (13).

Treatment-related mortality in induction chemotherapy with cytarabine in combination with daunorubicin occurs in about 3 to 7% of AML patients, with being the most frequent cause of mortality blood stream infections, and gram-negative rods and opportunistic fungi being the main culprits (7,14). In another study by Kayal et al., it was found that 66.7% of AML patients undergoing induction therapy died because of an infection (9).

Within infectious complications post-induction therapy, there are a wide range of infections, spanning from bloodstream infections that may be linked to severe sepsis to fungal infections commonly manifesting as respiratory tract infections or persistent

febrile neutropenia (7). Fungemia, cellulitis, typhlitis, mucositis, colitis and urinary tract infections (UTI) are some other frequent infectious complications that AML patients endure (15).

Diagnosis and treatment of infections in neutropenic patients are still a challenge (***Table 3***). Despite developing life-threatening infections, symptoms and signs are minimal, because of neutropenia, thus hindering an early diagnosis and adequate treatment (11).

The incidence of infectious complications can be reduced using prophylactic antibacterial, antiviral, and antifungal agents; however, it remains increased (11). Since most patients experience long-term antimicrobial exposure, there is an increased risk of adverse effects, drug-drug interactions, added costs, altered gut microbiome, and infections with multidrug-resistant organisms requiring shifts in management strategies (10). Furthermore, infections often cause delays and dose reduction in chemotherapy protocols, consequently decreasing the chances of success (14).

Table 3. Summary of tests in infections diagnosis. *Adapted from (16).*
** Invasive tests for respiratory infections diagnosis will be performed depending on the clinical status of the patient and the risk of developing complications.*

Blood test
Blood counts, ions, renal and hepatic function. CPR and/or PCT.
Microbiological tests (for bacterial infections)
CVC and peripherical vein cultures, urine analysis and culture, and culture of the samples extracted from the infection focus* (sputum, CRL, pleural liquid, peri catheter exudate, cutaneous lesions biopsy), fecal culture, *Clostridium difficile* toxin determination in feces, *Legionella* and *Streptococcus pneumoniae* antigen detection in urine.
Imaging
Thorax X-ray.
Other tests
High-resolution thoracic, paranasal sinuses, cerebral or abdominal CT. Fundus examination.

3.2 Endothelium

The endothelium is a highly dynamic and heterogenic organ with metabolic, immunologic, inflammatory, barrier, hemostatic, vascular, and synthetic functions. Its dysfunction is key in the pathogenesis of many acute and chronic diseases, infections, cancer, heart failure, and metabolic and autoimmune disorders, among many others (17).

Endothelium is in the interface between the blood/lymph and vessel wall, with a luminal surface composed of quiescent endothelial cells that remains anticoagulant, and anti-adherent (18–20). Endothelial cells are highly affected by their microenvironment and detect modifications in blood pressure, mechanical frictional forces, shear stress, circulating chemical messengers or neighbor cells chemical messengers, and interaction with platelets or leukocytes, and respond to these changes by modulating their structure and function and releasing a wide range of factors (***Table 4***) to ultimately regulate permeability, cell growth and migration, platelet function, cell interaction, and inflammation (20,21).

Table 4. Endothelial functions and molecules that participate in each of them. *Adapted from (22).*

Function	**Substance**	
Coagulation	Tissular factor, von Willebrand factor, platelet activation factor.	
Anticoagulation	Glycosaminoglycans, thrombomodulin, thrombin receptor, S protein, tissue factor pathway inhibitor (TFPI), prostacyclin.	
Vasodilation	Nitric oxide, prostacyclin, bradykinin, endothelium-derives hyperpolarizing factor.	
Vasoconstriction	Endothelin, thromboxane A2, angiotensin-II, free radicals.	
Fibrinolytic	Tissue-type plasminogen activator (t-PA), single chain urokinase-type plasminogen activator (scu-PA), plasminogen (Plg) receptor, urokinase-type plasminogen activator (u-PA) receptor.	
Antifibrinolytic	t-PA inhibitor.	
Inflammation	**Cytokines**	IL-1 β, IL-6, IL-8, TNF-α, interferon-γ.
	Leukocyte adhesion	Selectins P and E, ICAM-1, ICAM-2, VCAM-1.
	Adhesion proteins	Von Willebrand factor, type IV collagen, fibronectin, vitronectin, thrombospondin, elastin.

Inflammation, infectious agents, or biochemical alterations lead to endothelial activation; therefore, the endothelium changes its phenotype to pro-inflammatory and pro-thrombotic to defend the organ from aggression. If the stimulus is intense and persistent enough, endothelial activation transforms into endothelial dysfunction, resulting in a disproportion of relaxing and contracting factors, procoagulant and anticoagulant mediators or growth-inhibiting and promoting substances, ultimately leading to pathological proinflammatory, prothrombotic, and vasoconstrictive states, with added cell adhesion and oxidative stress (23). Causes that may induce endothelial dysfunction may be: decreased nitric oxide (NO) production and/or bioavailability, increased oxidative stress, decreased prostacyclin levels, and inflammatory responses (overexpression of cellular adhesion molecules and secretion of chemokines) (24).

3.2.1 AML and endothelial dysfunction

Endothelial cells of the bone marrow sinusoids participate in the regulation of the migration of cells between the bone marrow and the blood circulation by providing a vascular network. Bone marrow endothelial cells constitutively express E-selectin, VCAM-1, von Willebrand factor, and CD-34 (ligand of L-selectin). Myeloblasts induce their own adhesion to the vascular endothelium by activating the endothelial cells through secretion of TNF-α and IL-1β and the direct contact between both endothelial cells and myeloblasts adhesion receptors (***Figure 2***). Hematopoietic stem cells express P-selectin glycoprotein ligand-1, CD44, E-selectin receptor, Very Late Antigen 4 (VLA-4), and Lymphocyte Function-associated Antigen 1 (LFA-1), to migrate to bone marrow stroma through the endothelium (4,25).

The interactions between AML and endothelial cells promote angiogenesis. VEGF was found to be high in AML patients, with increased angiogenesis and decreased apoptosis rate (4).

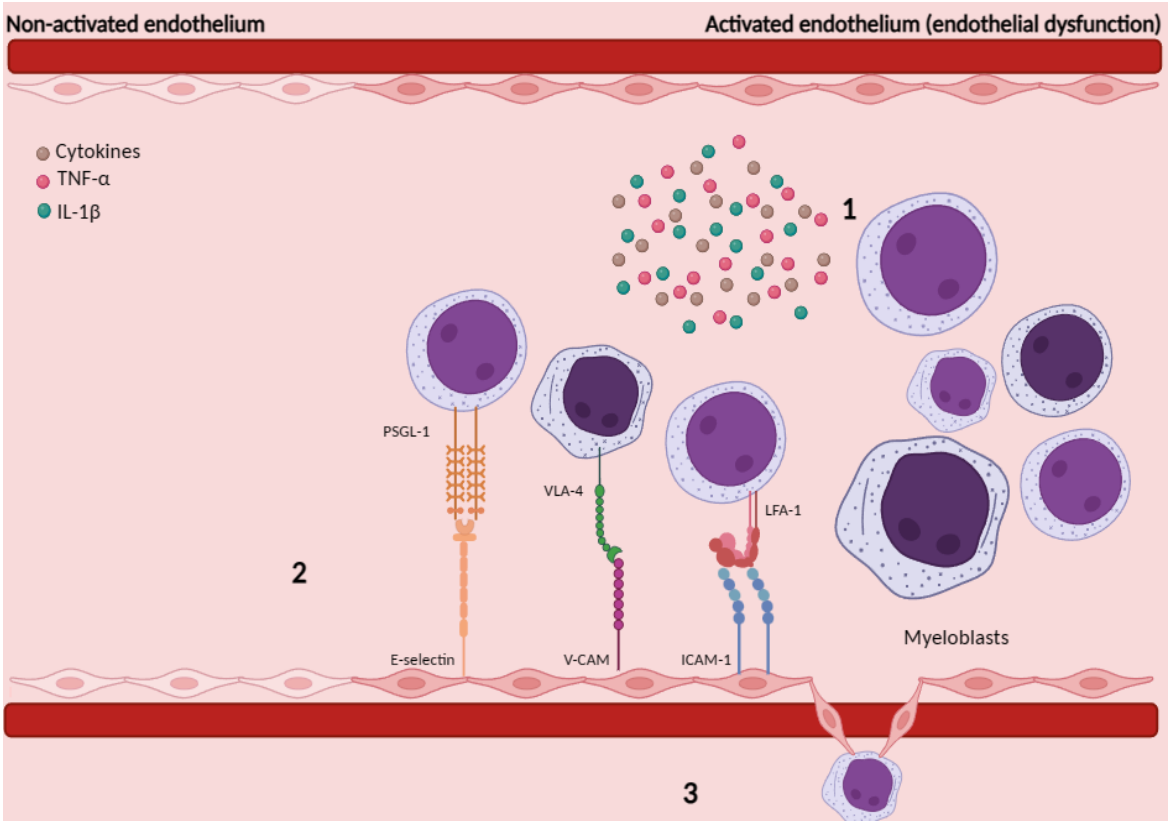


Figure 2. Endothelial dysfunction in AML. *1. Myeloblasts release cytokines, TNF-α and IL-1β to promote their adhesion to endothelial cells. 2. Endothelial cells express E-selectin, V-CAM and ICAM-1, and myeloblasts express PSGL-1, VLA-4, and LFA-1 to bind to endothelial cells. 3. Myeloblasts transmigrate through endothelium.*

3.2.2 Chemotherapy and endothelial dysfunction

As previously mentioned, the standard treatment for AML involves intensive induction chemotherapy with anthracycline and cytarabine. This treatment can worsen the pancytopenia caused by the disease itself.

Additionally, several articles have studied the role of chemotherapy in endothelial dysfunction.

Anthracyclines decrease levels of nitric oxide (NO) and endothelin-1 (ET-1) while increasing the production of reactive oxygen species (ROS) in the mitochondria. This leads to mitochondrial damage, dysfunction, and the subsequent release of cytochrome c, which activates caspases - proapoptotic factors responsible for the apoptosis of vascular endothelial cells (21,26). Cytarabine-arabinoside is another

primary drug used in AML. However, it can induce capillary leak syndrome, which increases capillary endothelium permeability. This results in the augmented extravasation of fluid and protein through the endothelium, leading to diffuse pitting edema, non-cardiogenic pulmonary edema, or exudative serous cavity effusions (pleura and pericardium) (4).

Systemic and local inflammation induces the release of cytokines and the expression of intercellular adhesion molecules (ICAM) on the surface of endothelial cells, which promote the transmigration of leukocytes. Increased vascular permeability also exposes underlying tissue to chemotherapeutic agents. Eventually, chemotherapy promotes vascular inflammation, reduces vasodilation, and increases vascular permeability (26).

3.2.3 Endothelial cell dysfunction and infections, sepsis and multiorgan failure

Infection is the first inflammatory response to a microbial invasion. If it persists, it can progress to sepsis, which is defined as a “life-threatening organ dysfunction caused by a dysregulated host response to infection” (27); septic shock and multiorgan failure syndrome, which is the concurrent dysfunction of two or more organs (13,28).

The pathophysiology of sepsis and MODS is primarily due to the imbalanced activation of pro-inflammatory and anti-inflammatory immune responses, resulting in the abundant release of cytokines, mediators, and molecules, and activation of coagulation cascades (29,30).

Additionally, the endothelium plays a crucial role in the pathophysiology of sepsis and MODS, serving as a barrier between the bloodstream and tissues.

When a microorganism infects a host, the endothelium is triggered by LPS (produced by gram-negative bacteria), pathogen-associated molecular patterns (PAMPs), and endogenous damage-associated molecular patterns (DAMPs) through activation of TLRs in endothelial cells, monocytes, and antigen-presenting cells. As a result, endothelial cells release cytokines, chemokines, and procoagulant factors, and overexpress adhesion molecules (13,30,31).

All these effects will ultimately cause significant phenotypic modulation of the endothelium, shifting to a procoagulant, proadhesive, proinflammatory, and proapoptotic phenotype. Additionally, damage to the glycocalyx and dysfunction of vascular tone can impair microcirculatory blood flow, increase permeability (interstitial leakage), and cause tissue hypoperfusion, leading to organ injury and potentially life-threatening organ failure (13,31).

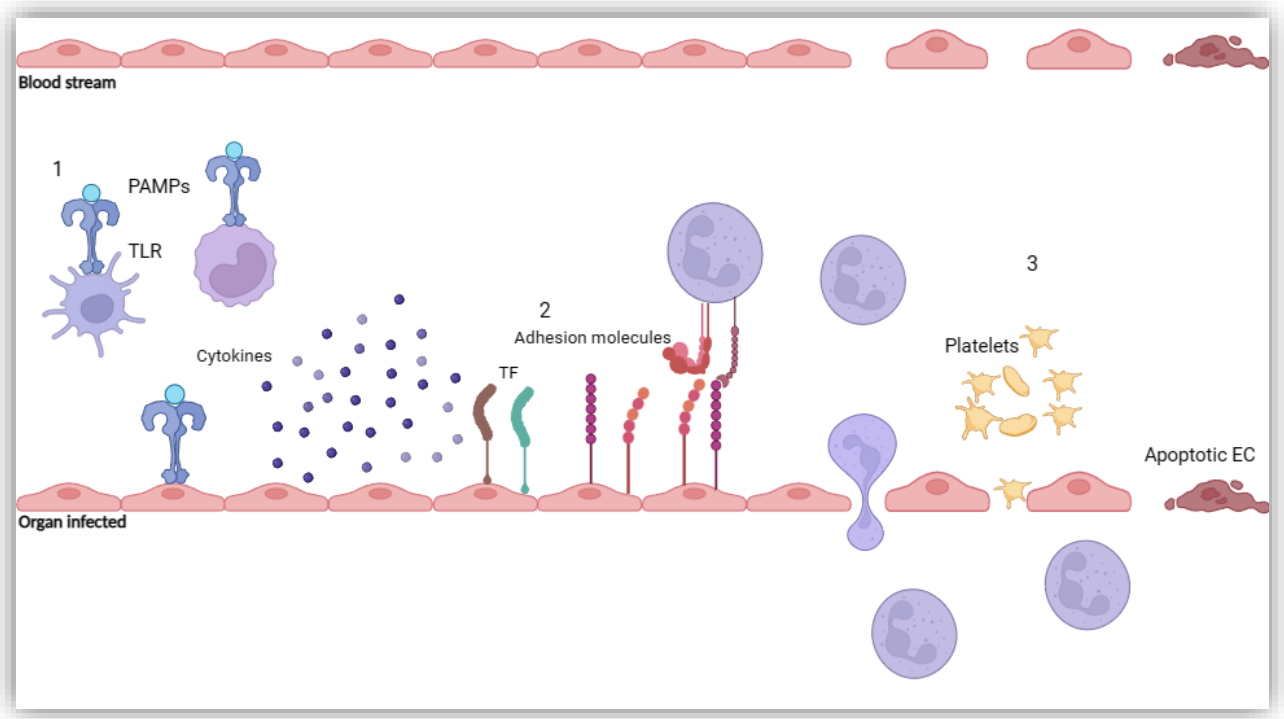


Figure 3. Endothelial dysfunction and sepsis. *Endotoxins, PAMPs and DAMPs activate TLRs of EC, monocytes and antigen presenting cells, and trigger the endothelium (1). EC release cytokines procoagulant factors (such as TF) and overexpress adhesion molecules (2). Endothelial damage induces an increase in permeability, with consequent leakage and a change in endothelial phenotype into a proadhesive, proapoptotic, procoagulant, proinflammatory phenotype, leading to organ dysfunction in which endothelium is present (3).*

3.2.4 Endothelial dysfunction in Hematopoietic stem cell allogenic transplant

AML is the most frequent indication for allo-HCT, and It is performed during the first remission (32). A transplant preparative regimen must be done before allo-HCT, to avoid graft rejection. Both myeloablative conditioning and reduced intensity conditioning will ablate completely (MAC) or not (RIC) the bone marrow, increasing the risk of infections (33). During HPT, the endothelium is affected by the conditioning

therapy, immunosuppressors, proinflammatory molecules released by cells and injured tissues, endotoxins that translocated through the injured mucosal barriers, leukocyte implant, and immune reactions in allo-HCT related to alloreactivity.

The first consequence of this aggression is the physiological activation of the endothelium. If these stimuli persist and are intense enough, they can lead to endothelial dysfunction. This, in turn, can cause post-transplant endothelial syndromes that may be life-threatening for the patient.

Post-transplant endothelial syndromes, such as graft-versus-host disease and sinusoidal obstructive syndrome (***Table 5***), are clinical manifestations of endothelial dysfunction that occur in allo-HCT, and normally appear during the first 30 to 60 days post allo-HCT (32). The signs and symptoms are highly similar among them, which difficult the differential diagnosis. A precocious diagnosis and treatment are required, because of their severity, and to avoid their transition into a multiorganic failure or multiorganic dysfunction syndrome.

Table 5. *Post-transplant endothelial syndromes. Adapted from (32).*

Post-transplant endothelial syndromes
• Fluid overload syndrome
• Capillary leak syndrome
• Sinusoidal obstruction syndrome
• Pre-engraftment syndrome
• Engraftment syndrome
• Transplant associated thrombotic microangiopathy
• Vascular idiopathic pneumonia syndrome
- Diffuse alveolar hemorrhage
- Capillary pulmonary hyperpermeability syndrome
- Peri-engraftment respiratory distress syndrome
• Posterior reversible encephalopathy syndrome
• Acute graft-versus-host disease

3.3 Endothelial Activation and Stress Index

Endothelial dysfunction plays a pivotal role in the pathophysiology of post-transplant endothelial syndromes. As these are life-threatening conditions, a validated biomarker is needed to predict their outcome or onset. Therefore, the Endothelial and Stress Index was developed. (34).

EASIX is a score based on three laboratory parameters commonly used in clinical practice: The formula for EASIX is (LDH × creatinine/platelet count) (34). LDH, creatinine, and platelet count. These parameters are associated with endothelial stress and dysfunction. High levels of LDH are released during endothelial damage by circulating cells and endothelial cells. Endothelial dysfunction can contribute to acute renal failure and glomerulonephritis, resulting in increased creatinine levels. Thrombotic microangiopathies and chronic graft-versus-host disease have been associated with low platelet counts, which are linked to endothelial activation and clotting (34).

EASIX was used to determine its predictive ability for overall survival in patients with acute graft-versus-host-disease after undergoing an allogenic hematopoietic transplant. The study demonstrated that EASIX was a strong predictor of both overall survival and non-relapse mortality in acute GVHD (34). Additionally, when EASIX was assessed before conditioning, it also correlated with overall survival after allo-HCT (35). Several studies have assessed the predictive ability of EASIX in allo-HCT. These studies have shown that EASIX is a good predictor for various major complications related to allo-HCT, such as transplant-associated thrombotic microangiopathy, acute GVHD (35), sinusoidal obstruction syndrome (36), and sepsis (37).

Considering that endothelial dysfunction not only participates in the pathophysiology of allo-HCT-related complications, but further studies were also made to assess the ability of EASIX score as a prognosis marker of survival and complications of several diseases.

EASIX was assessed as a predictor of ICANS and CRS, complications related to CAR-T therapy, after CAR-T infusion, and the results showed that EASIX is indeed a predictor

of CRS and ICANS post-CAR-T-infusion and validated the capacity of pre-EASIX to predict the risk of ICANS and CRS (38,39).

Furthermore, EASIX was also proven to predict complications and mortality in COVID-19 patients with and without hematological malignancy (40,41), advanced liver disease (42); and overall survival in lower-risk MDS (43), multiple myeloma (44), and diffuse large B-cell lymphoma (45).

4. Justification

Acute myeloid leukemia is the most usual form of leukemia in adults. Although there is a cure for the disease, the prognosis remains poor (46), due to complications related to the treatment, specifically intensive chemotherapy.

Globally, the incidence and mortality of AML have been steadily increasing, with 80000 deaths per year (46,47). It is expected that this trend will continue in 2040, with mortality doubling (47).

Infections are the most common and potentially lethal complication of intensive chemotherapy due to the pancytopenia caused by the treatment. Eventually it complicates into to sepsis and multiorganic failure, which leads to death (7–9,13). Among AML patients who undergo intensive induction therapy, 95% experience infectious complications, with bacterial infections being the most frequent. Treatment-related mortality occurs in 3 to 7% of AML patients, with approximately half dying due to infections.

Investigations have been conducted to determine the risk of death or lethal complications in AML, to reduce treatment-associated mortality rates, such as antimicrobial and antifungal prophylaxis. However, the incidence of infectious complications remains high.

Several studies have been conducted to better understand the physiology of sepsis and multiorgan failure syndrome, with a focus on improving patient management. These studies have revealed that endothelial cells play a significant role in the pathophysiology of these conditions (13,30,31). Additionally, a recent study demonstrated the crucial role of endothelial cells in the pathophysiology of AML and its complications (4).

Luft et al. developed the Endothelial and Stress Index (EASIX), a score that determines endothelial dysfunction. This simple formula consists of (LDH × creatinine/platelet count). The EASIX score has demonstrated the ability to predict complications and mortality in acute graft-versus-host disease, a complication of allogenic hematopoietic

transplants. This is due to the association between endothelial dysfunction and the pathophysiology of these diseases (34).

To this extent, further studies have validated the predictive ability of EASIX in various conditions such as ICANS and CRS associated with CAR-T infusion, overall survival in multiple myeloma, diffuse large B-cell lymphoma, and COVID-19, among others (40–45). However, no investigation was made to validate the EASIX in AML.

Considering all of this, we propose a multicenter retrospective cohort study to validate the EASIX as a predictor of infectious complications related to intensive chemotherapy that AML patients will undergo. If the study demonstrates that EASIX is a predictor of infectious complications associated with intensive chemotherapy, there could be a change in the management of the patients with a high EASIX score, meaning they may require more aggressive treatment of infections to prevent the development of multi-organ failure syndrome and subsequent mortality.

5. Hypothesis

5.1 Primary hypothesis

The EASIX score is a predictor of severe infections in AML patients that undergo intensive chemotherapy.

5.2 Secondary hypothesis

The EASIX score is associated to treatment related mortality in 28 days.

The EASIX score is associated to CR and/or CRI.

6. Objectives

6.1 Primary objective

Analyze the EASIX score as a predictor of severe infectious complications in newly diagnosed AML patients that undergo intensive chemotherapy.

6.2 Secondary objectives

To determine whether EASIX associates with treatment related mortality in 28 days.

To determine if EASIX associates with CR and/or CRI.

7. Methodology

7.1 Study design

The design consists of a prospective cohort study. The study will be coordinated by the CETLAM group, and lead by the hematology unit of the Institut Català d'Oncologia (Josep Trueta Hospital), Girona.

7.2 Study population

The study will include all the patients newly diagnosed of AML, in the CETLAM centers, that will undergo intensive chemotherapy.

7.2.1 Inclusion criteria

The patients that were eligible to be included in the study were:

- Age ≥18 years old.
- Patients who signed the informed consent.
- Patients with an ECOG score ≤2 (***Table 8***).
- Patients diagnosed with AML de *novo*, according to 2022 ICC (48) (***Figure 4***) and/or 2022 WHO criteria (5) (***Table 1***).
- Patients treated according to 2022 CETLAM protocol (***Annex 1***).

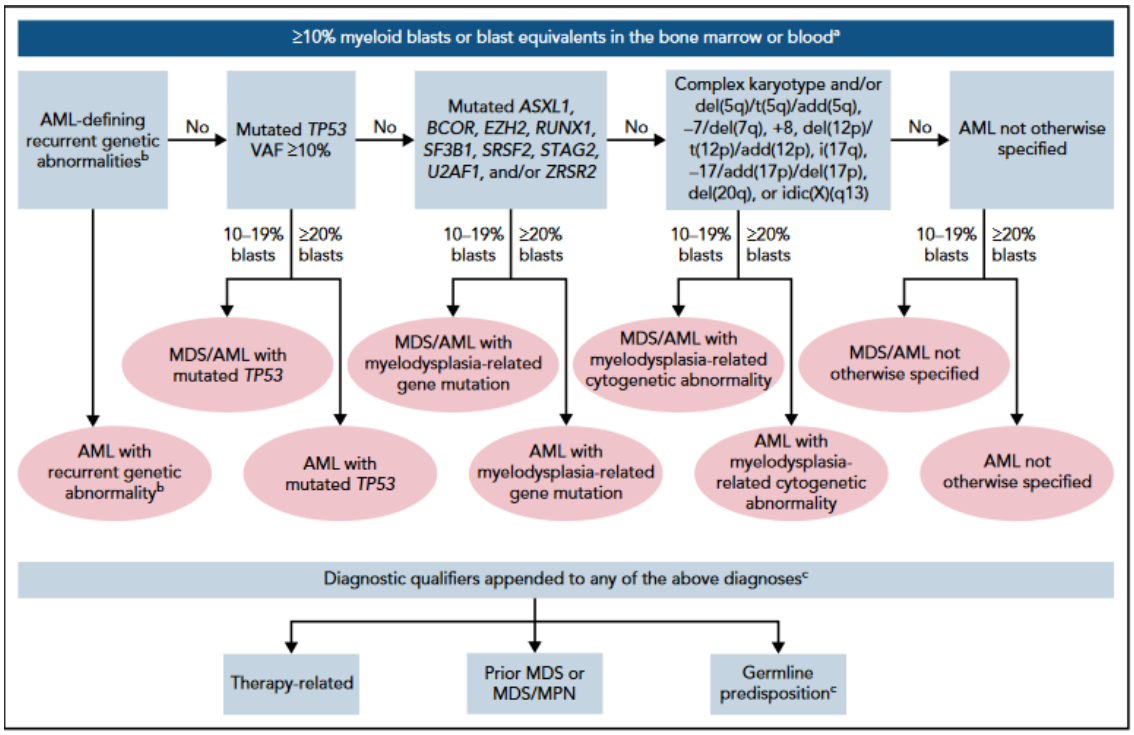


Figure 4. Hierarchical classification of the 2022 International Consensus Classification of AML. *Obtained from (48).*

7.2.2 Exclusion criteria

The patients that were excluded from this study are:

- Patients diagnosed with Acute Promyelocytic Leukemia (APL).
- AML patients who were considered not eligible for intensive treatment, according to Ferrara criteria (***Table 6***) (49).
- Patients who reject to participate in the study.
- AML secondary to treatment (they do another treatment).
- Pregnant patients.
- Patients that fulfill 2022 CETLAM protocol exclusion criteria (50):
    - If AML treatment was given prior to study inclusion. Treatment will be accepted
    - with hydroxyurea at the required dose
    - Chronic Myeloid Leukemia blast crisis. AML cases with *BCR:ABL* rearrangement can be included.
    - Presence of other uncontrolled neoplastic diseases, in active treatment or those with a risk of recurrence of more than 50% in the first year after the end of treatment. It will not be considered exclusion criteria:
        - Squamous or basocellular cutaneous carcinoma.
        - Cervix carcinoma *in situ*.
        - Breast cancer *in situ*.
        - Incidental prostate cancer histological finding.
    - Renal failure, with creatinine levels ≥2,5 times the normal value and/or RGF <35 ml/hour, except when it is due to AML.
    - Anormal hepatic function, with Child B o C hepatic cirrhosis or bilirubin levels 2,5 times the normal value, except when these alterations are due to AML.
    - Patients with ejection fraction lower that 45%, symptomatic cardiac failure, or both.
    - Sever pulmonary disease, with DCLO <65% and/or VEF1 <65%, or with oxygen therapy requirement.
    - Non-controlled active infection, including CHV, BHV and HIV. It is allowed inclusion to the protocol to those patients who have the infection controlled.

Table 6. Ferrara criteria of patients considered unfit to conventional intensive chemotherapy. *Adapted from (49).*

1.	Advanced age (over 75 years)
2.	Severe cardiac comorbidity
3.	Severe pulmonary comorbidity
4.	Severe renal comorbidity
5.	Severe hepatic comorbidity
6.	Active infection resistant to anti-infective therapy
7.	Cognitive impairment
8.	Low performance status (ECOG functional scale)
9.	Any other comorbidity that the physician judges to be incompatible with chemotherapy

7.3 Sampling

7.3.1 Sample size

Accepting an alpha risk of 0.05 and a power of 0.8 in a two-tailed test fifty-eight subjects are necessary to recognize as statistically significant a Relative Risk greater than or equal to 1.5. An incidence rate in the non-exposed group has been estimated to be 0.66. A drop-out rate of 10% has been anticipated.

7.3.2 Sample selection

The sample will be obtained through a consecutive non-probabilistic method. All the patients diagnosed of AML in a hospital that collaborates with CETLAM, will be offered to participate in the study, if they meet the inclusion but not exclusion criteria, after being informed and signed the informed consent.

CETLAM

The CETLAM group, funded in 1988, is an association that designs and promotes protocols of investigation and treatment of AML high risk MDS. The following hospitals from all over Spain collaborate in this association (50):

- Balears
    - Hospital Son Llàtzer
    - Hospital Son Espases
- Barcelona

  - Hospital de la Santa Creu i Sant Pau
  - Hospital Universitari Vall d'Hebron
  - Hospital Clínica Universitari de Barcelona
  - Hospital del Mar
  - Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol
  - Hospital Mútua Terrassa
  - Hospital de Sabadell Corporació Sanitària Parc Taulí
  - Institut de Recerca contra la Leucèmia Josep Carreres
  - Institut Català d'Oncologia-Hospital Duran i Reynals
  - Hospital Universitari de Bellvitge
  - Hospital Sant Joan de Déu
  - Hospital General de Granollers
  - Hospital Universitari
  - Fundació Althaia de Manresa
  - Hospital Universitari Sagrat Cor
  - Hospital Moisés Broggi de Sant Joan Despí
  - Consorci Sanitari de Terrassa
  - Hospital Universitari Consorci Hospitalari de Vic
  - Hospital Sant Joan de Déu de Manresa
- Girona
  - Institut Català d'Oncologia-Hospital Universitari Dr. Josep Trueta
- Lleida
  - Hospital Universitari Arnau de Vilanova
- Tarragona
  - Institut Català d'Oncologia-Joan XXIII
  - Institut Català d'Oncologia-Hospital Verge de la Cinta
- Coruña
  - Hospital Juan Canalejo
- Valencia
  - Hospital Clínico de Valencia
- Madrid

  - Hospital Universitario La Paz
  - Hospital General Universitario Gregorio Marañón
- Màlaga
  - Hospital Clínico de Málaga
- Murcia
  - Hospital Morales Meseguer
- Sevilla
  - Hospital Universitario Virgen del Rocío

7.4 Variables

7.4.1 Independent variable

EASIX: EASIX is a discrete continuous variable that will be calculated with the formula LDH (Ul/l) × creatinine (mg/dl) / platelet count (10^3/mcL). It will be then categorized into a dichotomous qualitative variable since a cut off for the score will be calculated. Thus, EASIX is a dichotomous qualitative variable that is expressed as higher or lower than the EASIX score cut off.

7.4.2 Primary dependent variable

Severe infection: The dependent variable of the primary objective is the infections that produce hemodynamic instability, resulting in sepsis and multiorganic failure, leading to the death of the patient. This is a dichotomous qualitative variable expressed as yes or no.

Infections definition and classification according to the fourth version of the Common Terminology Criteria for Adverse Events (CTCAE) is explained in ***Annex 2***.

7.4.3 Secondary dependent variable

Treatment related mortality in 28 days: Is the dependent variable of the secondary objective, which is defined as death that occurs during the 28 days, counting from the start of the intensive chemotherapy. It is a dichotomous qualitative variable expressed as yes or no and measured by percentage.

Complete response (CR): Is the dependent variable of the secondary objective, defined in *Table 6*. Dichotomous qualitative variable expressed as yes or no.

Complete response with incomplete hematologic recovery (CRI): Is the dependent variable of the secondary objective, defined in ***Table 7***. Dichotomous qualitative variable expressed as yes or no.

Table 7. Response criteria in AML. *Obtained from (48).*

Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/µL); platelet count ≥100 × 10^9/L (100 000/µL).
Complete response with incomplete hematologic recovery (CRI)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/µL]) or thrombocytopenia (<100 × 10^9/L [100 000/µL]).

7.4.4 Covariates

Demographic variables

Age: Continuous quantitative variable expressed in years. This study includes patients from ≥18 years old.

Sex: Dichotomous qualitative variable expressed as male or female.

Clinical variables

Eastern Cooperative Oncology Group performance status (ECOG): Score that assesses the functional status of the patient with a malignant disease, that ranges from 0 to 5 (51). It is a categorical qualitative variable expressed as a number from 0 to 5 (***Table 8***).

Table 8. ECOG Score. *Obtained from (51).*

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead.

Sequential Organ Failure Assessment (SOFA): Index that reflects the severity of organ dysfunction in the context of critical illnesses (52). It evaluates six items from 0 to 4, each of those items correspond to an organ system, with a final score ranging from 0 to 24. It is a discrete quantitative variable (***Table 9***).

Table 9. SOFA Score. *Obtained from (52).*

Organ System, Measurement	**SOFA Score**				
	0	1	2	3	4
Respiration PaO2/FiO2 mmHg	>400	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets x10^3/mcL	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dl)	<1,2	1,2-1,9	2-5,9	6-11,9	>12
Cardiovascular MAP or vasopressor requirement	>70	<70	Dopamine ≤5 µg/kg/min or dobutamine (any dose)	Dopamine >5 µg/kg/min or Epinephrine ≤0.1 µg/kg/min or Norepinephrine ≤0.1 µg/kg/min	Dopamine >15 µh/kg/min or Epinephrine >0.1 µg/kg/min or Norepinephrine >0.1 µg/kg/min
CNS Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Creatinine, (mg/dl) or Urine output	< 1,2	1,2–1,9	2–3,4	3,5–4,9 (or urine output <500 ml/day)	>5; urine output < 200 ml/day

Acute Physiology and Chronic Health Evaluation II (APACHE-II): Scoring system that assesses severity of illness and risk of mortality of critically ill patients upon admission to an ICU (53) (***Table 10***).

Table 10. APACHE II Score. *Adapted from (53).*

Physiologic Variable	**Points**								
	+4	+3	+2	+1	0	+1	+2	+3	+4
1. Temperature (ºC)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
2. MAP (mmHg)	≥160	130-159	110-129				50-69		≤49
3. Heart Rate (/min)	≥180	140-179	110-139				55-69	40-54	≤39
4. Respiratory Rate (/min)	≥50	35-49		25-34		10-11	6-9		≤5
5. Oxygenation (mmHg) a. A-aDO2 if FiO2 ≥0,5 b. PaO2 FiO2 <0,5	500	350-499	200-349			61-70		55-60	<55
6. Acid-base balance a. Arterial pH b. Serum HCO_3 (mEq/l) if no arterial blood gas	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9			7.25-7.32 18-21.9	7.15-7.25 15-17.9	<7.15 <15
7. Sodium (mEq/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
8. Potassium (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
9. Creatinine (mEq/l)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
10. Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<2.5
11. WBC (×1000/mm3)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
12. GCS	Score = 15 minus actual GCS								
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6									
C. Chronic Health Points*									
Total APACHE II Score (add together the points from A+B+C)									
* Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immune compromised as defined below, assign points as follows: 5 points for non-operative or emergency post-operative patients 2 points for elective post-operative patients									

Laboratory variables

The following laboratory values are continuous quantitative variables:

- **Hematology**

- **Platelet count**: Expressed as 10^3 /mcL.
- **Leucocyte count**: Expressed as 10^3 /mcL.
- **Neutrophil count**: Expressed as 10^3 /mcL.
- **International normalized ratio (INR)**: Standardized measure of the clotting ability of blood-based on the ratio of an individual's prothrombin time to the normal mean prothrombin time, used especially to monitor the risk of bleeding in patients receiving anticoagulant therapy (54).
- **Activated partial thromboplastin time (TTPa)**: Parameter that evaluates the intrinsic clotting pathway (55). Expressed as seconds.
- **Fibrinogen**: Expressed as mg/dl.

- **Blood chemistry**

- **Creatinine**: Expressed as mg/dl.
- **Lactate Dehydrogenase (LDH)**: Expressed as Ul/l.
- **Potassium (K), sodium (Na)**: Expressed as mEq/l.
- **Venous lactate**: Expressed as mg/dl.
- **PAFI ratio**: Oxygenation index calculated by the formula PaO2/FIO2, that is used in patients suspected to have any degree of respiratory distress (56).
- **C reactive protein (CRP)**: Expressed as mg/dl.
- **Procalcitonin (PCT)**: Expressed as ng/dl.
- **Ferritin**: Expressed as ng/ml.

Blood cultures: Dichotomous qualitative variable that is defined by presence or not of germens, expressed as yes or no.

7.5 Data collection

Diagnosis

This is a prospective multicenter study that will be conducted from January 2024 to December 2025.

All patients diagnosed with AML who meet the Ferrara criteria for the treatment of choice of AML and meet the inclusion criteria (but not the exclusion criteria) are eligible to enter the CETLAM 2022 protocol.

After being given all information regarding the study, patients will be offered the opportunity to participate. If they agree, the patient must sign an informed consent form. The hematologist will collect demographic information, perform a physical examination, check vital signs, and calculate the ECOG score. A numerical code will be assigned to the patient to anonymize the information before registering it in the CETLAM database.

Since this study is multicenter, the database will include information on all patients from the collaborating hospitals. However, investigators will only have access to information from their center.

Six time points were established to collect the data. Diagnosis (day 0), hospitalization (induction therapy days 1 and 7; follow-up days 14, 21, and 28), and end of hospitalization (day >28).

Hospitalization

Induction therapy

Upon admission for induction therapy on day one, a general physical examination, vital signs check, and blood tests (**hematology** and **blood chemistry**) will be performed. ECOG, SOFA, and APACHE-II scores will also be calculated. The information will be transmitted to the database. The induction therapy infusion will begin afterwards.

On the seventh day, the final doses of induction therapy will be administered. The same blood tests, physical examination, and vital signs will be conducted, and the ECOG, SOFA, and APACHE-II scores will be calculated. Additionally, the first EASIX score will be determined. All information will be transmitted to the database.

Follow-up

Blood tests, physical examinations, and vital signs will be taken on days 14, 21, and 28. ECOG, SOFA, APACHE-II will be calculated. EASIX scores will be calculated at all three time points.

End of hospitalization

Hospitalization will end upon receipt of the discharge report or in the event of the patient's death. ECOG, SOFA, APACHE-II, and EASIX scores will be calculated before discharge.

Table 11. Summary of data collection from day zero (diagnosis) to twenty-eight.
** Color pink cells represent the tests that will be made if patient presents symptoms or is suspected of infection.*

	Diagnosis	**Hospitalization**					**End of hospitalization**
		Induction therapy		**Follow-up**			
	D0	D1 (±1)	D7 (±1)	D14 (±1)	D21 (±1)	D28 (±1)	>D28
Confirm eligibility criteria							
Informed consent							
Demographic data							
ECOG							
Vital signs checking							
Hematology							
Blood chemistry							
Blood cultures							
Catheter culture							
Imaging							
SOFA							
APACHE II							
EASIX							

8. Statistical analysis

Statistical analysis will be performed with Statistical Package for the Social Science (SPSS) software for Windows®. Sample size calculation has been defined in Methods section (***7.3.1 Sample size***).

8.1 Descriptive analysis

A descriptive analysis will be conducted for all variables. Quantitative variables will be summarized using either the mean and standard deviation (for normal distribution) or the median and interquartile range (for non-normal distribution). Qualitative variables will be summarized as proportions with a 95% confidence interval.

An EASIX score cut-off will be determined using the ROC curve with 'severe infections' as the endpoint. For each calculated EASIX score, sensitivity and specificity will be calculated. A ROC curve will be created using sensitivity and (1-specificity) values, and the Area Under the Curve will be calculated. The chosen score cutoff should strike a balance between specificity and sensitivity, meaning it should have both the highest sensitivity and specificity with the highest AUC.

$$\textbf{Sensitivity} = \frac{True\ Positive}{True\ Positive\ +\ False\ negative}$$

$$\textbf{Specificity} = \frac{True\ Negaitive}{True\ Negative\ +\ False\ Positive}$$

Equation 1. *Sensitivity and specificity.*

8.2 Bivariant inference

To determine the differences in variables between patients with high and low EASIX scores, we will use a chi-squared test for qualitative variables and a student's t-test for quantitative variables with a normal distribution. For quantitative variables without a normal distribution, we will use the Mann-Whitney U test.

8.3 Multivariant analysis

Following the bivariate analysis, a multivariate analysis will be conducted, adjusting for co-variables to avoid potential confounders that could alter the results and for variables that differed at baseline.

To evaluate the association between the independent variable and the dependent variables, a Cox regression model will be used, with the calculation of hazard ratios to estimate the risk of different outcomes. A p-value of less than 0.05 will be considered statistically significant.

The multivariate analysis will be adjusted for the following confounders:

- **Fever at the time of diagnosis**: It could affect the score since it is a sign of infection. If the patient already has an infection before starting chemotherapy, the EASIX score could be higher.
- **Chemotherapy tolerance**: Chemotherapy-related toxicity can vary between patients, with some experiencing more adverse effects than others. The use of chemotherapy agents in AML treatment has been shown to cause endothelial dysfunction, which may result in a higher EASIX score for patients with increased toxicity.
- **Neutropenia**: A longer duration of neutropenia increases the risk of infection and complications.
- **Pre-existing comorbidities**: Patients with multiple comorbidities may not be suitable for treatment due to the intensity and risk of toxicity. This study excludes patients who are ineligible according to the Ferrara criteria, which includes the presence of comorbidities. Therefore, patients with comorbidities are not included in this study to avoid confusion.
- The **SOFA** and **APACHE-II scores** were assessed before starting the treatment. If the patient is already hemodynamically unstable, it indicates significant endothelial dysfunction, which may result in a higher EASIX score.
- It may not be possible to calculate the **EASIX score** at all time points, for example, if the patient passes away.

9. Ethical aspects

The main investigators and collaborators ensure that the study will be conducted under the ethical principles outlined in the World Medical Association Declaration of Helsinki of 'Ethical Principles for Medical Research Involving Human Subjects', revised in October 2013, and will respect the ethical principles of Beauchamp and Childress as follows:

- **Autonomy** is ensured because all participants will receive the subject information sheet (***Annex 3***) and the informed consent document (***Annex 4***) which contains detailed information about the study. If they choose to participate, they must provide their informed consent by signing the document, in accordance with the law "Ley orgánica 41/2002, 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica". Participants retain the right to withdraw from participation at any point (***Annex 5***).
- **Non-maleficence** is ensured by providing all participants with the same treatment as patients with the same diagnosis who did not participate in the study. No medication will be administered that is not part of the habitual clinical practice.
- **Beneficence** is also a key consideration. This study aims to determine the predictive value of EASIX in AML patients with life-threatening infections. This will help to better understand the cause of death in these patients and to optimally manage their cases to avoid further complications.
- To ensure **justice**, only patients who meet the inclusion criteria and not the exclusion criteria, and who are willing to participate, will be included in the study, avoiding any form of discrimination.

The research protocol will be evaluated by the Comitè Ètic d'Investigació Clínica (CEIC) of Hospital Universitari Doctor Josep Trueta and the other participating hospitals. If objections arise, necessary modifications will be made to meet their conditions. The study will commence only after receiving their approval.

The personal data of patients included in the study database will be treated confidentially in accordance with Regulation (EU) 2016/679 of the European

Parliament and of the Council of April 2016 on the protection of natural persons concerning the processing of personal data and on the free movement of such data, as well as the “Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales”.

To maintain data confidentiality, each patient will be assigned a unique identification number in the database for anonymous analysis. Access to the data will be restricted to the researchers overseeing the study and the information will only be used for the study. Participants can request the removal of their data from the database at any time. All data, including any adverse events, will be published transparently. The researchers declare no conflicts of interest in this study.

10. Limitations

Study design

As this is an observational study, we expect confounding bias to occur. To reduce potential confounding, both bivariate and multivariate analysis will be performed with all potential confounders (detailed explanation in ***8.3 multivariant analysis***).

As this is a prospective cohort study, there is a risk of losing participants due to early death (before 28 days) or refusal to continue in the study. However, a dropout rate of 10% was assumed in the sample size calculation. All withdrawals and situations where the patient could not be followed up are recorded.

There will be several meetings during the study to ensure that the study is progressing correctly.

Sampling and sample size

This study will use a non-probabilistic, consecutive sampling method, which carries the risk of selecting a non-representative sample, leading to selection bias. To minimize this bias, the inclusion and exclusion criteria have been designed to ensure that the target population is well-defined.

Although our required sample is fifty-eight, the study will be multicentered due to the design and sampling method complying with some limitations while extrapolating the study in other patients, so doing the study multicenter through will increase the external validity of the study.

11. Working plan and chronogram

The study will be conducted under the CETLAM protocol. The research team (RT) consists of:

- **Principal Investigator (PI)**: Hematologist Dr Rosa Coll Jordà, who will oversee patient recruitment, hospitalization, data collection, interpretation of results and writing and publication of articles.

- **Sub-investigators (SI)**: A hematologist from each participating hospital will be responsible for data collection and will be involved in patient care with their team.

- **Hematology Team (HT)**: Each investigator (PI or SI) will work with his/her team of fellow hematologists who will be involved in patient care, follow-up and will help with data collection.

- **Collaborators (C)**: Nurses, clinical analysis team, radiology team.

- **Statistician (ST)**: Responsible for the statistical analysis of the data in the database.

This study, which will last approximately three years, from November 2023 to March 2026, will progress through the following phases (***Table 12***):

STAGE 0: Protocol design

The PI and the student (S) will conduct a comprehensive literature review to establish the background, primary and secondary hypotheses, and objectives of the study. A research protocol will be developed, including a thorough explanation of the variables and objectives of the study, together with the definition of the analytical framework. This phase will take approximately 2 months.

STAGE 1: Ethical approval

The research protocol will be submitted to the CEIC. This stage will take about 3 months, until the CEIC answers whether it can be carried out.

STAGE 2: Coordination

The PI and his research team will have a meeting with other CETLAM centers to present and explain the protocol and ask for their collaboration. They will also discuss patient recruitment, data collection, and database entry. A hematologist from each hospital

will be appointed for patient recruitment, data collection, and database entry. During the whole process, PI and co-investigators will get reunited twice a year to discuss the evolution of study and solve any doubts that may arise.

STAGE 3: Patients' recruitment

Recruitment of patients to participate in the study will begin. They will be given a subject information sheet and an informed consent document if they agree to participate (further explanation in ***diagnosis***). This process will start in March 2024 and end in December 2025, as patients will be recruited as they are diagnosed.

STAGE 4: Hospitalization and data collection

On admission, patients will receive intensive induction chemotherapy. During this period of hospitalization and follow-up, hematologists will collect data and enter it into the database (detailed explanation ***hospitalization***). The hematology team will monitor the treatment, perform follow-up, and discharge the patient when fully recovered (hematologically and/or clinically). This process will start in March 2024 and end in December 2025.

STAGE 5: Statistical analysis

A statistician will analyze all the data collected. This process will take two months. The results will then be given to the PI.

STAGE 6: Article elaboration and diffusion

The interpretation of the results, the discussion, and the conclusion will be done by the research team (PI and CI) and later written in an article. It is expected that the article will be submitted to the journal of choice in 2026.

Table 12. Chronogram.

STAGES	STAFF	2023		2024						2025				2026			
		Nov	Dec	Jan	Feb	Mar	Apr-Agu	Sept	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sept	Oct-Dec	Jan	Feb	Mar	Apr-Dec
STAGE 0: Protocol design																	
Bibliographic research	PI, S																
Protocol elaboration	PI																
STAGE 1: Ethical approval																	
CEIC submission, evaluation and approval	PI																
STAGE 2: Coordination																	
Coordination meetings	PI, SI																
STAGE 3: Patients' recruitment																	
Information and informed consent	PI, SI																
STAGE 4: Hospitalization and data collection																	
Initiation of treatment	PI, SI, C, HT																
Data collection and database input	PI, SI																
Follow-up	PI, SI, C, HT																
STAGE 5: Statistical analysis																	
Data analysis	ST																
STAGE 6: Article elaboration																	
Interpretation of the results	PI, SI, HT																
Final report elaboration	PI, SI, HT																
Paper publication and diffusion	PI																

12. Budget

The research team and staff are employed by the Josep Trueta Hospital and there is no need to hide any staff for our function. Therefore, there will be no additional costs for staff in the budget. They will be responsible for collecting the data for the study and entering it into the database.

This study will use the CETLAM 2022 protocol database, so there will be no need for a data manager to create the database.

A statistical expert will be required for data analysis due to the lack of knowledge in this area in the team. It is estimated that 30 hours of work will be required, paid at 35€/h. The total cost will be 1050€.

Medical material, equipment and treatments needed for the treatment will be provided by the National Health System, as this study will follow the already established treatment and management of AML.

All the blood tests, blood cultures and radiological tests that will be carried out on the patients will not exceed those that are already routinely carried out on these patients while they are in hospital. The national health system will therefore cover the costs.

Hospitalization costs will also be covered by the National Health System, as the period of hospitalization ends when the patients are medically authorized to be discharged.

11.6 will be needed to print information sheets and informed consent documents, at a cost of 0.1€ per copy.

Once the study is completed, it will be disseminated to the scientific community. All data collected will be reported in a scientific paper to be published in open access scientific journals. Publication costs are estimated at 2000€.

Logistics and inscription fees for assisting to the congress would be approximately 1500€.

Table 13. Budget.

Item	Amount	Cost	Subtotal
PERSONNEL EXPENSES			
Statistician	30 hours	35€ per hour	1050€
Principal investigator and Co-investigator	-	0€	0€
MATERIAL COSTS			
Informed consent and subject information sheet	116 copies	0,1€ per copy	11,6€
Blood tests, cultures, X-rays, CT, AML drugs	-	0€	0€
ARTICLE DIFFUSION COST			
Publication fees	-	2000€	2000€
Congress fees	-	1500€	1500€
		Total	**4561,6€**

13. Feasibility

We believe that our study is feasible for the following reasons:

Of the staff needed to carry out the study (hematologists, clinical analysis technicians, nurses, radiologists), the statistician will only represent an additional cost, as he is not part of the hospital staff already working there. Therefore, the hematologists will collect the data and enter them into the database, and the statistician will analyze them.

The hematologists will oversee the treatment and overall management of the patients during their hospital stay. They are experts in the field.

The treatment will be the standard treatment already used in normal clinical practice, without the use of experimental drugs, which means that the National Health Service will provide the drugs, medical equipment and materials, so there will be no extra cost and no risk to the patients, in accordance with ethical principles.

The database that will be used is CETLAM, in which all the hospitals participating in the study will enter their data, which will make it easier for all the hospitals to collect the same data and reduce the risk of errors.

14. Impact

To date, no study has evaluated the predictive ability of the EASIX score for serious infections in AML patients receiving intensive chemotherapy. Therefore, this is the first study to investigate this hypothesis.

If our hypothesis is confirmed, it would provide valuable insights into the factors that contribute to the death of certain AML patients with infections despite receiving the same treatment (intensive chemotherapy).

In addition, being able to predict which patients are more prone to severe infections could have a significant impact on the management of these patients:

- Choosing more effective antibiotic strategies that prevent life-threatening infections, thereby reducing infection-related mortality.

- Reducing patients' morbidity, thereby improving their quality of life and enabling them to complete treatment.

- Increased treatment tolerance and ability to tolerate the intensity of treatment and start consolidation therapy earlier. Less treatment-related mortality.

In summary, with this study, there could be a reduction in life-threatening infections and subsequent death, treatment-related mortality and treatment- and/or infection-related morbidity.

15. Bibliography

1. Provan D, R. J. Singer C, Baglin T, Dokal I. Manual oxford de Hematología Clínica. 3a edición. Madrid: Grupo Aula Médica; 2010.

2. Vakiti A, Mewawalla P. Acute Myeloid Leukemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Dec 1]. p. 1–7. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507875/

3. DiNardo CD, Erba HP, Freeman SD, Wei AH. Acute myeloid leukaemia. The Lancet [Internet]. 2023 Jun 17 [cited 2023 Dec 12];401(10393):2073–86. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00108-3/fulltext

4. Fodil S, Arnaud M, Vaganay C, Puissant A, Lengline E, Mooney N, et al. Endothelial cells: major players in acute myeloid leukaemia. Blood Reviews [Internet]. 2022 Jul 1 [cited 2023 Nov 26];54:1–12. Available from: https://www.sciencedirect.com/science/article/pii/S0268960X22000066

5. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia [Internet]. 2022 Jul [cited 2023 Dec 22];36(7):1703–19. Available from: https://www.nature.com/articles/s41375-022-01613-1

6. Poh C, Alobeidi E, Tuscano J, Rosenberg A, Hoeg R, Jonas B. Complications in Acute Myeloid Leukemia Inductions Prior to Count Recovery: A Feasibility Study for Outpatient Care at an Academic Center. Blood [Internet]. 2020 Nov 5;136:1–6. Available from: https://www.researchgate.net/publication/346691452_Complications_in_Acute_Myeloid_Leukemia_Inductions_Prior_to_Count_Recovery_A_Feasibility_Study_for_Outpatient_Care_at_an_Academic_Center

7. Tober R, Schnetzke U, Fleischmann M, Yomade O, Schrenk K, Hammersen J, et al. Impact of treatment intensity on infectious complications in patients with acute myeloid leukemia. J Cancer Res Clin Oncol [Internet]. 2023 [cited 2023 Dec 19];149(4):1569–83. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10020242/

8. Kayal S, Sengar M, Jain H, Bonda A, George B, Kulkarni UP, et al. Induction Related Mortality in Acute Myeloid Leukemia: Multivariate Model of Predictive Score from the Indian Acute Leukemia Research Database (INwARD) of the Hematology Cancer Consortium (HCC). Blood [Internet]. 2019 Nov 13 [cited 2023 Dec 20];134(Supplement_1):1–6. Available from: https://doi.org/10.1182/blood-2019-127623

9. Kayal S, Jain H, Nayak L, Thorat J, Bhattacharyya J, Das D, et al. Induction Related Mortality Score in Acute Myeloid Leukemia: Prospective Validation Study (pRISM) of the Hematology Cancer Consortium (HCC). Blood [Internet]. 2022 Nov 15 [cited 2023 Dec 17];140(Supplement 1):3223–4. Available from: https://doi.org/10.1182/blood-2022-169001

10. Logan C, Koura D, Taplitz R. Updates in infection risk and management in acute leukemia. Hematology [Internet]. 2020 Dec 4 [cited 2023 Dec 15];2020(1):135–9. Available from: https://doi.org/10.1182/hematology.2020000098

11. Rusu RA, Sîrbu D, Curşeu D, Năsui B, Sava M, Vesa ŞC, et al. Chemotherapy-related infectious complications in patients with Hematologic malignancies. J Res Med Sci [Internet]. 2018 Jul 26 [cited 2023 Dec 19];23:1–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6091125/

12. Mabrey FL, Gardner KM, Shannon Dorcy K, Perdue A, Smith HA, Davis AM, et al. Outpatient intensive induction chemotherapy for acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood Advances [Internet]. 2020 Feb 19 [cited 2023 Dec 20];4(4):611–6. Available from: https://doi.org/10.1182/bloodadvances.2019000707

13. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood [Internet]. 2003 May 15 [cited 2023 Dec 27];101(10):3765–77. Available from: https://doi.org/10.1182/blood-2002-06-1887

14. Mulanovich V, Kontoyiannis DP. Acute myeloid leukemia and the infectious diseases consultant. Leukemia & Lymphoma [Internet]. 2018 Jun 3 [cited 2024 Jan 9];59(6):1284–91. Available from: https://doi.org/10.1080/10428194.2017.1365861

15. Jalbut MM, Brunner AM, Amrein PC, Ballen KK, Hobbs GS, Perry AM, et al. Early infectious complications among patients treated with induction compared to hypomethylating therapy for acute myeloid leukemia. Leuk Lymphoma [Internet]. 2018 Apr 1 [cited 2023 Dec 17];59(4):988–91. Available from: https://europepmc.org/articles/PMC6197051

16. Batlle M, Jiménez-Pérez M. Infecciones bacterianas. In: Manual de trasplante hematopoyético y terapia celular. 6th ed. Barcelona: Mediúscula, mitjans educatius S.L.; 2022. p. 485–8.

17. Ambrosino P, Grassi G, Maniscalco M. Endothelial Dysfunction: From a Pathophysiological Mechanism to a Potential Therapeutic Target. Biomedicines [Internet]. 2021 Dec 31 [cited 2023 Dec 7];10(78):1–4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8773018/

18. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. Intensive Care Med [Internet]. 2010 Aug 1 [cited 2023 Dec 7];36(8):1286–98. Available from: https://doi.org/10.1007/s00134-010-1893-6

19. Badimón L, Martínez-González J. Endotelio en la protección vascular: nuevos conocimientos. Rev Esp Cardiol [Internet]. 2002 Jul 2 [cited 2023 Dec 7];55:17–26. Available from: http://www.revespcardiol.org/en-endotelio-proteccion-vascular-nuevos-conocimientos-articulo-13035740

20. Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial Cells in Physiology and in the Pathophysiology of Vascular Disorders. Blood [Internet]. 1998 May 15 [cited 2023 Nov 30];91(10):3527–61. Available from: https://www.sciencedirect.com/science/article/pii/S0006497120546727

21. Soultati A, Mountzios G, Avgerinou C, Papaxoinis G, Pectasides D, Dimopoulos MA, et al. Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications. Cancer Treat Rev [Internet]. 2012 Aug;38(5):473–83. Available from: https://www.cancertreatmentreviews.com/article/S0305-7372(11)00198-8/fulltext

22. Duboscq C. Endotelio vascular. Hematología [Internet]. 2017 [cited 2023 Nov 30];21:19–30. Available from: https://www.sah.org.ar/revistasah/numeros/vol21/extra/07-Vol%2021-extra.pdf

23. Cau SBA, Evora PRB, Tostes RC. Chapter 9 - Vasoconstrictor Substances Produced by the Endothelium. In: Da Luz PL, Libby P, Chagas ACP, Laurindo FRM, editors. Endothelium and Cardiovascular Diseases [Internet]. London: Academic Press; 2018 [cited 2023 Dec 11]. p. 115–25. Available from: https://www.sciencedirect.com/science/article/pii/B978012812348500009X

24. Elmarakby AA, Pollock DM, Imig JD. 6.25 - Renal Dysfunction in Hypertension and Obesity. In: Taylor JB, Triggle DJ, editors. Comprehensive Medicinal Chemistry II [Internet]. Oxford: Elsevier; 2007 [cited 2023 Dec 11]. p. 575–95. Available from: https://www.sciencedirect.com/science/article/pii/B008045044X001875

25. Ladikou EE, Sivaloganathan H, Pepper A, Chevassut T. Acute Myeloid Leukaemia in Its Niche: the Bone Marrow Microenvironment in Acute Myeloid Leukaemia. Curr Oncol Rep [Internet]. 2020 Feb 11 [cited 2023 Dec 9];22(3):1–9. Available from: https://doi.org/10.1007/s11912-020-0885-0

26. Terwoord JD, Beyer AM, Gutterman DD. Endothelial dysfunction as a complication of anti-cancer therapy. Pharmacology & Therapeutics [Internet]. 2022 Sep 1 [cited 2023 Dec 7];237:1–38. Available from: https://www.sciencedirect.com/science/article/pii/S0163725822000109

27. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA [Internet]. 2016 Feb 23 [cited 2023 Dec 28];315(8):801–10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4968574/

28. Zhao P yue, Xia Y, Tao Z bo, Li S yan, Mao Z, Yang X peng, et al. Global Research Status of Multiple Organ Dysfunction Syndrome During 2001–2021: A 20-Year Bibliometric Analysis. Frontiers in Medicine [Internet]. 2022 [cited 2023 Dec 28];9:1–14. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2022.814381

29. Asim M, Amin F, El-Menyar A. Multiple organ dysfunction syndrome: Contemporary insights on the clinicopathological spectrum. Qatar Med J [Internet]. 2020 Sep 22 [cited 2023 Dec 26];2020(1):1–16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884906/

30. Jarczak D, Kluge S, Nierhaus A. Sepsis—Pathophysiology and Therapeutic Concepts. Front Med (Lausanne) [Internet]. 2021 May 14 [cited 2023 Dec 28];8:1–22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8160230/

31. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial Responses in Sepsis. Am J Respir Crit Care Med [Internet]. 2020 Aug [cited 2023 Dec 28];202(3):361–70. Available from: https://www.atsjournals.org/doi/full/10.1164/rccm.201910-1911TR

32. Síndromes por disfunción endotelial posTPH. In: Manual de trasplante hematopoyético y terapia celular. 6th ed. Barcelona: Mediúscula, mitjans educatius S.L.; 2022. p. 295–6.

33. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood [Internet]. 2014 Jul 17 [cited 2023 Dec 19];124(3):344–53. Available from: https://doi.org/10.1182/blood-2014-02-514778

34. Luft T, Benner A, Jodele S, Dandoy CE, Storb R, Gooley T, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. The Lancet Haematology [Internet]. 2017 Sep 1 [cited 2023 Dec 11];4(9):e414–23. Available from: https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(17)30108-4/fulltext

35. Luft T, Benner A, Terzer T, Jodele S, Dandoy CE, Storb R, et al. EASIX and mortality after allogeneic stem cell transplantation. Bone Marrow Transplant [Internet]. 2020 Mar;55(3):553–61. Available from: https://www.nature.com/articles/s41409-019-0703-1

36. Jiang S, Penack O, Terzer T, Schult D, Majer-Lauterbach J, Radujkovic A, et al. Predicting sinusoidal obstruction syndrome after allogeneic stem cell transplantation

with the EASIX biomarker panel. Haematologica [Internet]. 2021 Feb 1;106(2):446–53. Available from: https://haematologica.org/article/view/9631

37. Korell F, Schreck N, Müller-Tidow C, Dreger P, Luft T. Pre-transplant EASIX and sepsis after allogeneic stem cell transplantation. Intensive Care Med [Internet]. 2022 [cited 2023 Dec 1];48(6):753–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9012907/

38. Korell F, Penack O, Mattie M, Schreck N, Benner A, Krzykalla J, et al. EASIX and Severe Endothelial Complications After CD19-Directed CAR-T Cell Therapy-A Cohort Study. Front Immunol [Internet]. 2022 [cited 2023 Jun 27];13:1–10. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2022.877477/full

39. Greenbaum U, Strati P, Saliba RM, Torres J, Rondon G, Nieto Y, et al. The Easix (Endothelial Activation and Stress Index) Score Predicts for CAR T Related Toxicity in Patients Receiving Axicabtagene Ciloleucel (axi-cel) for Non-Hodgkin Lymphoma (NHL). Blood [Internet]. 2020 Nov 5 [cited 2023 Dec 12];136(Supplement 1):17–8. Available from: https://doi.org/10.1182/blood-2020-141388

40. Luft T, Wendtner CM, Kosely F, Radujkovic A, Benner A, Korell F, et al. EASIX for Prediction of Outcome in Hospitalized SARS-CoV-2 Infected Patients. Frontiers in Immunology [Internet]. 2021 [cited 2023 Dec 11];12:1–9. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2021.634416

41. Kalicińska E, Biernat M, Rybka J, Zińczuk A, Janocha-Litwin J, Rosiek-Biegus M, et al. Endothelial Activation and Stress Index (EASIX) as an Early Predictor for Mortality and Overall Survival in Hematological and Non-Hematological Patients with COVID-19: Multicenter Cohort Study. J Clin Med [Internet]. 2021 Sep 24 [cited 2024 Jan 26];10(19):1–16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8509351/

42. Schult D, Rasch S, Schmid RM, Lahmer T, Mayr U. EASIX Is an Accurate and Easily Available Prognostic Score in Critically Ill Patients with Advanced Liver Disease. J Clin Med [Internet]. 2023 Mar 28 [cited 2023 Dec 7];12(7):1–14. Available from: https://www.mdpi.com/2077-0383/12/7/2553

43. Merz A, Germing U, Kobbe G, Kaivers J, Jauch A, Radujkovic A, et al. EASIX for prediction of survival in lower-risk myelodysplastic syndromes. Blood Cancer J [Internet]. 2019 Nov 11 [cited 2023 Aug 14];9(11):1–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6848148/

44. Song GY, Jung SH, Kim K, Kim SJ, Yoon SE, Lee HS, et al. Endothelial activation and stress index (EASIX) is a reliable predictor for overall survival in patients with multiple myeloma. BMC Cancer [Internet]. 2020 Aug 24 [cited 2023 Nov 28];20(1):1–10. Available from: https://doi.org/10.1186/s12885-020-07317-y

45. Park S, Go SI, Lee GW. The Endothelial Activation and Stress Index (EASIX) score is an independent prognostic factor in patients with diffuse large B-cell lymphoma. BMC Cancer [Internet]. 2022 Jul 25 [cited 2023 Dec 15];22:1–9. Available from: https://doi.org/10.1186/s12885-022-09915-4

46. Yi M, Li A, Zhou L, Chu Q, Song Y, Wu K. The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: estimates based on the global burden of disease study 2017. Journal of Hematology & Oncology [Internet]. 2020 Jun 8 [cited 2024 Jan 3];13(1):1–16. Available from: https://doi.org/10.1186/s13045-020-00908-z

47. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet [Internet]. 2018 Nov 10 [cited 2024 Jan 3];392(10159):2052–90. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6227505/

48. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood [Internet]. 2022 Sep 22 [cited 2023 Dec 19];140(12):1345–77. Available from: https://doi.org/10.1182/blood.2022016867

49. Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia [Internet]. 2013 May [cited 2024 Jan 2];27(5):997–9. Available from: https://www.nature.com/articles/leu2012303

50. CETLAM. CETLAM Centros participantes [Internet]. 2018 [cited 2024 Jan 27]. Available from: https://www.cetlam.com/centrosColaboradores/index.php

51. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

52. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996 Jul;22(7):707–10.

53. Akavipat P, Thinkhamrop J, Thinkhamrop B, Sriraj W. Acute Physiology And Chronic Health Evaluation (APACHE) II Score – The clinical predictor in neurosurgical Intensive

Care Unit. Acta Clin Croat [Internet]. 2019 Mar [cited 2024 Jan 2];58(1):50–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6629196/

54. International normalized ratio ; 2012. In: The Free Dictionary [Internet]. Feasterville: Farlex; 2024 [cited 2024 Jan 3]. Available from: https://medical-dictionary.thefreedictionary.com/international+normalized+ratio

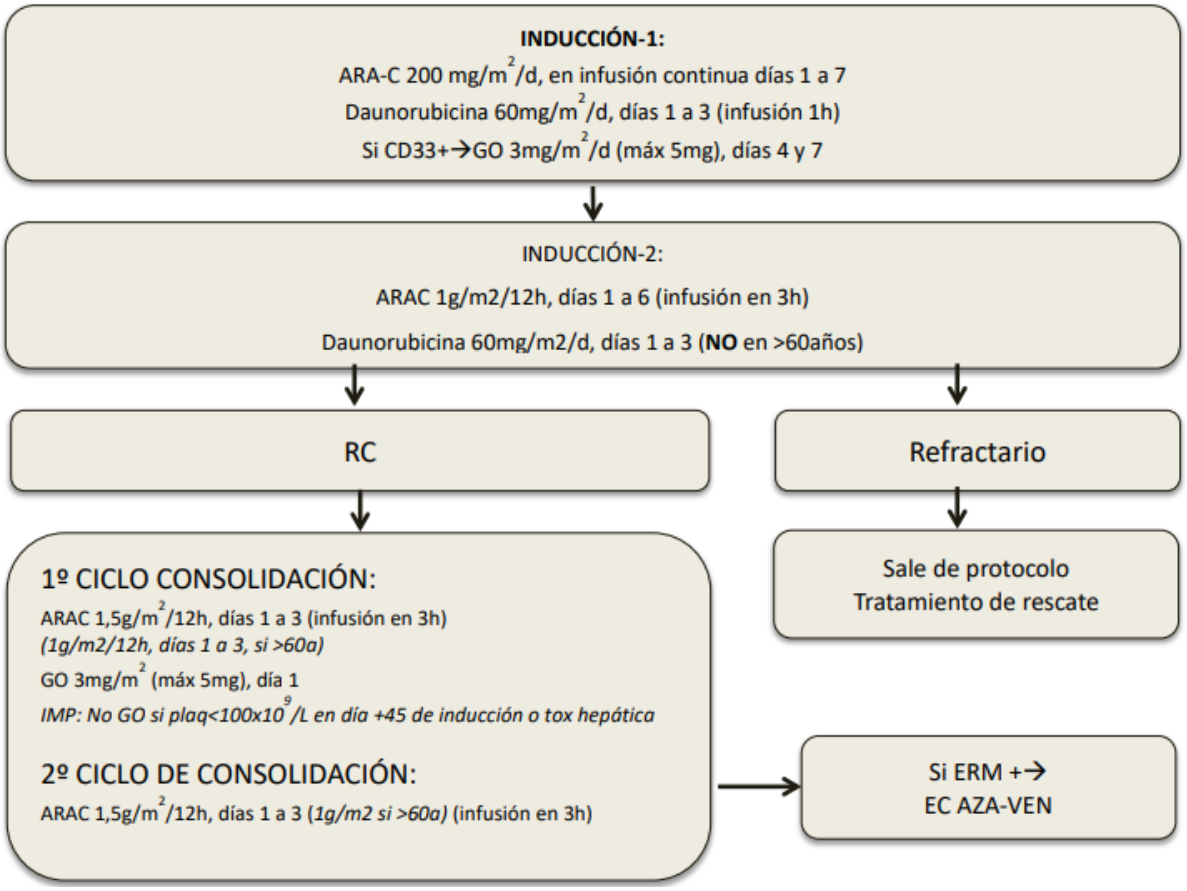
55. Rountree KM, Yaker Z, Lopez PP. Partial Thromboplastin Time. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Jan 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507772/

56. Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J, et al. A universal definition of ARDS: the PaO2/FiO2 ratio under a standard ventilatory setting—a prospective, multicenter validation study. Intensive Care Med [Internet]. 2013 Apr 1 [cited 2024 Jan 25];39(4):583–92. Available from: https://link.springer.com/article/10.1007/s00134-012-2803-x

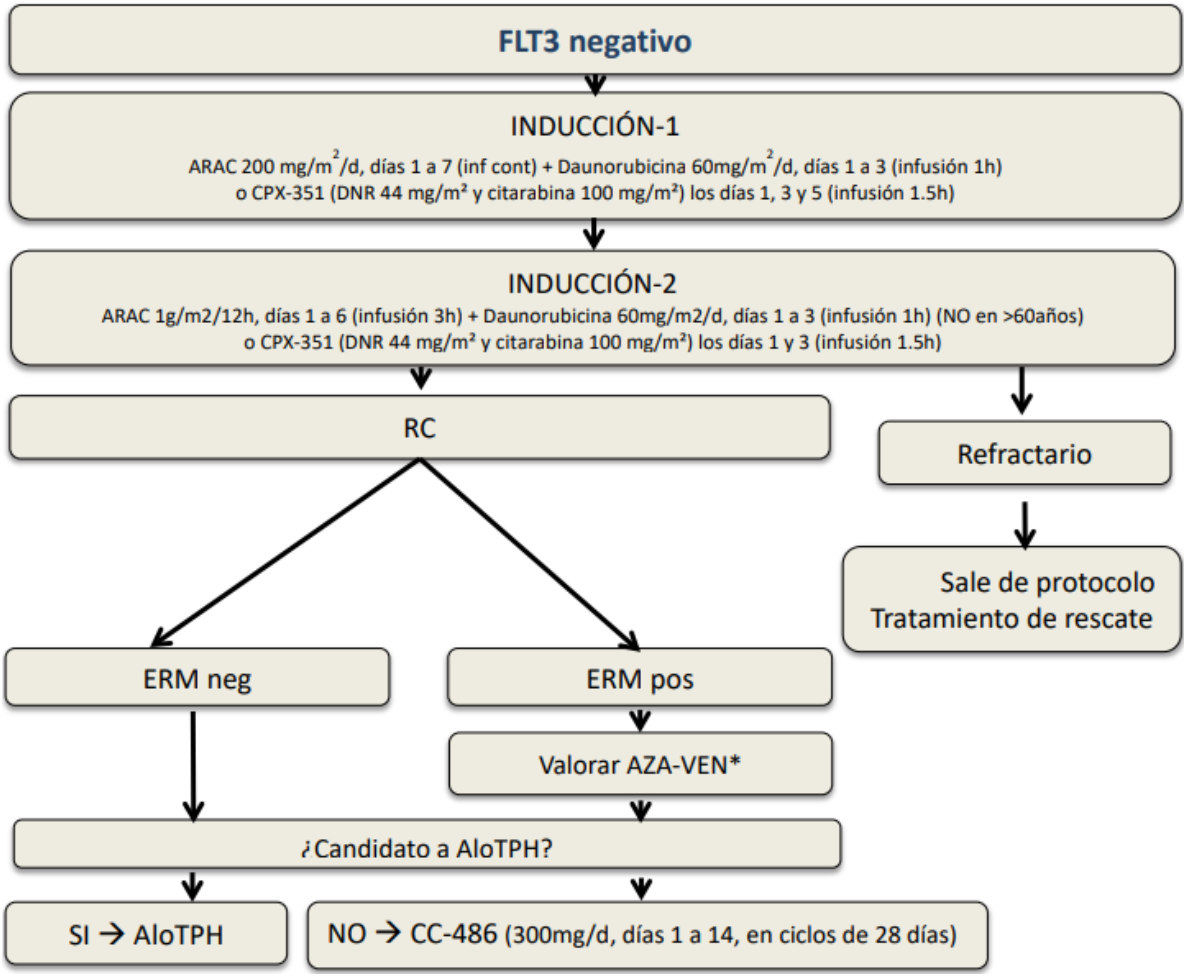
16. Annexes

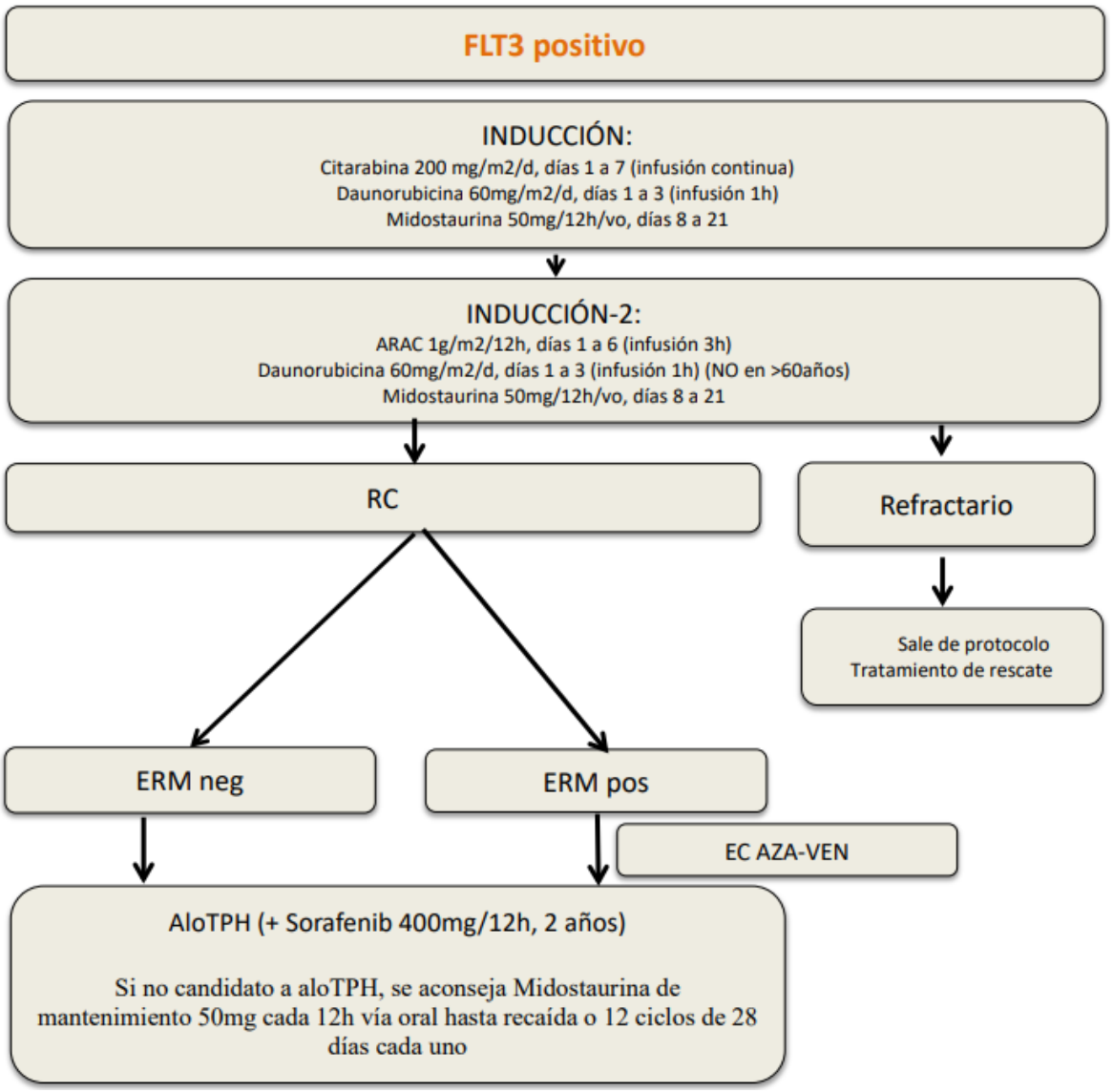
Annex 1: CETLAM protocol treatment

1. Pronóstico favorable



2. Pronóstico intermedio o advero




FLT3 positivo
INDUCCIÓN:
Citarabina 200 mg/m2/d, días 1 a 7 (infusión continua)
Daunorubicina 60mg/m2/d, días 1 a 3 (infusión 1h)
Midostaurina 50mg/12h/vo, días 8 a 21
INDUCCIÓN-2:
ARAC 1g/m2/12h, días 1 a 6 (infusión 3h)
Daunorubicina 60mg/m2/d, días 1 a 3 (infusión 1h) (NO en >60años)
Midostaurina 50mg/12h/vo, días 8 a 21
RC
Refractario
Sale de protocolo
Tratamiento de rescate
ERM neg
ERM pos
EC AZA-VEN
AloTPH (+ Sorafenib 400mg/12h, 2 años)
Si no candidato a aloTPH, se aconseja Midostaurina de mantenimiento 50mg cada 12h vía oral hasta recaída o 12 ciclos de 28 días cada uno

Annex 2: Infections classification

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity.					
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery.					
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract.					
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder.					
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast.					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi.					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use.					
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cecum.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes.					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea.					
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Device related infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum.					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or durationof illness >48 hrs; moderate abdominal pain	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines.					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an infectious process involving the esophagus.					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye.					
Gallbladder infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder.					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums.					
Hepatic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hepatitis viral	Asymptomatic, treatment not indicated	-	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma.					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles.					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an infectious process involving the kidney.					
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips.					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs.					
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum.					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord.					
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface.					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear.					
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life- threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp,and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an infectious process involving the pelvic cavity.					
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis.					
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat.					
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration alongthe course of the infected vein.					
Pleural infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura.					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock.					
Sinusitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses.					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin.					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
Soft tissue infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal.					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland.					
Scrotal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the spleen.					
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body).					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth.					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).					
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra.					
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra.					
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues.					

Infections and infestations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina.					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva.					
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound.					
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Annex 3: Subject information sheet

CETLAM
Grupo cooperativo de estudio y tratamiento de las leucemias agudas y mielodisplasias

HOJA DE INFORMACIÓN AL PACIENTE

Investigador Principal: Dra. Rosa Coll Jordà
CENTRO:
Título del protocolo: Análisis del índice EASIX como predictor de infecciones severes en el tratamiento de quimioterapia intensiva en los pacientes diagnosticados de Leucemia Aguda Mieloblástica.

1. INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio en el que se le invita a participar. El estudio ha sido aprobado por el Comité Ético de Investigación Clínica correspondiente. Nuestra intención es tan sólo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportunas.

2. PARTICIPACIÓN VOLUNTARIA

Este estudio está siendo realizado por investigadores de varios hospitales en España que colaboran con el grupo CETLAM (Grupo Cooperativo de Estudio y Tratamiento de las Leucemias Agudas y Mielodisplasias). El estudio ha sido aprobado por el comité de ética en investigación de los hospitales participantes.

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

3. DESCRIPCIÓN GENERAL DEL ESTUDIO

Usted ha sido diagnosticado de una leucemia mieloide aguda (LMA). Esta es una enfermedad neoplásica de la médula ósea cuyo tratamiento estándar es la quimioterapia.

Este estudio tiene como objetivo validar el índice EASIX (Endothelial Activation and Stress Index), una fórmula matemática basada en parámetros de laboratorio (plaquetas, creatinina, LDH), como predictor de las posibles complicaciones infecciosas severas que puedan derivar del tratamiento de la leucemia mieloide aguda.

Con la participación en este estudio le será realizado un estudio medular para el correcto diagnóstico de la enfermedad y recibirá el tratamiento habitual para la LMA, incluyendo los fármacos aprobados por las agencias para su uso en estas patologías. Asimismo, la participación en el estudio no conlleva un mayor número de exploraciones de las que se llevarían a cabo en caso de no participar en él.

El esquema diagnóstico y de tratamiento de su enfermedad hematológica consiste en:

3.1 **Estudio diagnóstico**:

Para el diagnóstico de la LMA se deberá realizar un estudio medular con la toma de muestras para el estudio morfológico, inmunofenotípico, genético y de biobanco (se le adjuntará la información del consentimiento informado del biobanco en un documento aparte).

Entre el resto de las pruebas diagnósticas necesarias, se realizará un examen físico y analítico y una ecografía cardíaca para determinar su función cardíaca.

3.2 **Tratamiento**:

Según los resultados del estudio medular y las características genéticas de la enfermedad, se establecerá el riesgo de esta en: favorable, intermedio o adverso. Con ello, se establecerá el esquema terapéutico que deberá seguir y que se detalla a continuación. Para la administración del tratamiento, será necesaria la colocación de una vía venosa central.

3.2.1 **Tratamiento de inducción**

Constará de 2 ciclos consecutivos de quimioterapia estándar con citarabina e idarubicina. A estos fármacos se le añadirá midostaurina en caso de presencia de mutación de *FLT3* o gemtuzumab en el primer ciclo en caso de conocer que se trata de una LMA de riesgo favorable o se realizará

tratamiento con vyxeos (formulación liposomal) en caso de tratarse de una LMA con cambios relacionados con la displasia.

3.2.2 Tratamiento de consolidación

- Pacientes de riesgo favorable: dichos pacientes recibirán dos ciclos de consolidación con citarabina añadiéndose gemtuzumab en la consolidación-1. En caso de la presencia de mutación de *FLT3-TKD,* se añadirá midostaurina en cada ciclo de quimioterapia
- Pacientes de riesgo intermedio o desfavorable: los pacientes pertenecientes a estos grupos de riesgo serán candidatos para recibir un trasplante alogénico una vez hayan alcanzado una respuesta completa tras el tratamiento de inducción. En ambos grupos de riesgo, podrán recibir entre 1 y 2 ciclos de consolidación con citarabina (o vyxeos si cumple indicación) en caso de que el equipo investigador lo considere necesario previo al trasplante alogénico. Del mismo modo que en anteriores ocasiones, en caso de mutación de *FLT3,* se añadirá a cada ciclo de tratamiento la midostaurina.

3.2.3 Tratamiento de mantenimiento

Se presentan 3 potenciales opciones de tratamiento de mantenimiento que dependerán de las condiciones de aprobación según las autoridades:

- Mantenimiento con midostaurina durante 1 año en pacientes sin indicación de trasplante alogénico y mutación de *FLT3*
- Mantenimiento con azacitidina oral en aquellos pacientes de riesgo intermedio o adverso, pero no candidatos a recibir trasplante alogénico
- Mantenimiento con sorafenib durante 2 años en aquellos pacientes que hayan recibido un trasplante alogénico y tengan la mutación de *FLT3*

3.3 Visitas y evaluaciones:

Durante los ciclos de quimioterapia ingresará en una planta de hematología para la administración del tratamiento y el seguimiento de las toxicidades. Asimismo, la necesidad de ingreso y los seguimientos será valorados por su equipo médico.

Una vez recuperada la toxicidad hematológica, será dado de alta para seguir controles ambulatorios con la frecuencia que su equipo médico estime oportuno.

Tras cada ciclo de quimioterapia, se realizará un estudio medular con la toma de muestras necesarias para hacer el seguimiento cercano de la respuesta al tratamiento y permitirá la toma de decisiones terapéuticas.

Una vez finalizado todo el tratamiento, se realizará un estudio medular cada 3 meses durante 3 años. De todos modos, la periodicidad de algunos estudios medulares puede verse alterada según decisión médica.

3.4 Diferencias frente al estándar de tratamiento

Este protocolo es asistencial e incluye todo el tratamiento en indicación para la LMA.

3.5 Preservación de fertilidad

Dado que el tratamiento quimioterápico puede provocar infertilidad, en la medida de lo posible, si la enfermedad no precisa inicio de tratamiento urgente y siempre a criterio del investigador, se podrán plantear técnicas de preservación de fertilidad.

3.6 Efectos secundarios habituales

Su médico le informará de los posibles efectos secundarios y toxicidades del tratamiento, y le resolverá todas las dudas que tenga al respecto. A modo de resumen, las principales toxicidades relacionadas con el tratamiento son:

Idarubicina: Los principales efectos tóxicos son náuseas y vómitos, mucositis, diarrea, aumento de las enzimas hepáticas, alopecia, toxicidad hematológica y toxicidad cardíaca (esta última es una toxicidad acumulativa).

Citarabina: La toxicidad más frecuente a las dosis convencionales consiste en náuseas y vómitos, diarrea, mucositis, alopecia, toxicidad hematológica, rash cutáneo.

Midostaurina: Las toxicidades más frecuentemente descritas son pancitopenia, cefalea, trastornos cardíacos, síntomas gastrointestinales, dermatitis y aumento de las enzimas hepáticas.

Sorafenib: Las toxicidades más frecuentemente descritas son citopenias, incremento de las pruebas de función hepática, toxicidad gastrointestinal en forma de náuseas y vómitos y alteraciones hidroelectrolíticas.

Azacitidina oral: las toxicidades más frecuentemente reportadas son la toxicidad gastrointestinal, dolor abdominal, artralgias, neutropenia mayor riesgo de infecciones y astenia.

4. BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Su participación en el estudio no implicará ninguna molestia adicional a las de la práctica asistencial habitual.

Usted no obtendrá ningún beneficio personal por su participación dentro de este protocolo más allá del beneficio terapéutico del tratamiento indicado. Su participación se realiza de forma voluntaria y altruista. Su único beneficio es el que corresponde al avance de la medicina y manejo de pacientes con LMA.

5. CONFIDENCIALIDAD

A partir del 25 de mayo de 2018 es de plena aplicación la nueva legislación en la Unión Europea (UE) sobre datos personales, en concreto el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD). El tratamiento, comunicación y cesión de sus datos se hará conforme a lo dispuesto en tal regulación y según la adaptación al reglamento general, la Ley orgánica 3/2018 de 5 de diciembre de Protección de Datos Personales y garantía de los derechos digitales.

Tanto el hospital como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá/n relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

Si se realizara alguna transferencia de sus datos codificados o fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o investigadores científicos que colaboren con CETLAM,

los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito y garantizando la confidencialidad como mínimo con el nivel de protección de la legislación vigente en nuestro país.

De acuerdo con lo que establece la legislación de protección de datos, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos en todo momento. Usted también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio.

Igualmente, tendrá derecho a retirar el consentimiento sobre el tratamiento de datos, no obstante, dicha retirada podría determinar su cese en la participación del estudio. Le recordamos que los datos no se pueden eliminar, aunque deje de participar en el estudio o aunque retire su consentimiento sobre el tratamiento de datos, para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos.

Para ejercitar sus derechos, diríjase a su médico del estudio.

Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho: https://www.aepd.es/es.

6. COMPENSACIÓN ECONÓMICA

No recibirá ninguna compensación económica por participar en este estudio.

7. OTRA INFORMACIÓN RELEVANTE

Si usted decide retirar el consentimiento para participar en este estudio, no se añadirá ningún dato nuevo a la base de datos

Annex 4: Informed consent form

CONSENTIMIENTO INFORMADO

Título: Análisis del índice EASIX como predictor de infecciones severes en el tratamiento de quimioterapia intensiva en los pacientes diagnosticados de Leucemia Aguda Mieloblástica.

Centro ***(indicar nombre del hospital)***: _____

Yo ***(indicar nombre del paciente)***, _____

He leído la hoja de información. Entiendo la información. He podido hacer preguntas adicionales. Han respondido satisfactoriamente a mis preguntas. Me han dado tiempo suficiente para decidir sobre la participación.

Sé que la participación es voluntaria. También sé que puedo decidir en cualquier momento no participar en el estudio o dejar de hacerlo y que no tengo que dar una razón para ello.

Doy mi consentimiento para que se informe a mi médico de cabecera y/o al especialista o los especialistas que me tratan de que estoy participando en este estudio.

Doy mi consentimiento para que mis datos se conserven en el hospital y por el promotor.

Declaro que he sido informado por el Médico después mencionado de:

□ Tratamiento para administrar

□ He comprendido la información recibida y podido formular todas las preguntas que he creído oportunas

□ Acepto el tratamiento

□ Acepto la realización de los estudios medulares necesarios

□ Acepto la toma de muestras para el biobanco

 He comprendido que la información referente a mi persona será tratada de forma confidencial y codificada de forma que quede protegida mi identidad. Y se me informa, que mis datos serán protegidos de acuerdo con el contenido de la Ley orgánica 3/2018 de 5 de diciembre de Protección de Datos Personales y garantía de los derechos digitales.

Nombre del paciente:

Firma: Fecha: _ / _ / _

Por la presente declaro que he informado completamente a este paciente sobre el estudio anterior.

Si se dispone de información durante el estudio que pueda influir en el consentimiento del paciente, se la comunicaré de manera oportuna.

Nombre del investigador (o su representante):

Firma: Fecha: _ / _ / _

Se recibió información adicional de (si procede):

Nombre:

Cargo:

Firma: Fecha: _ / _ / _

Annex 5: Withdrawal of consent form

REVOCACIÓN DEL CONSENTIMIENTO

Título: Análisis del índice EASIX como predictor de infecciones severes en el tratamiento de quimioterapia intensiva en los pacientes diagnosticados de Leucemia Aguda Mieloblástica.

Centro (indicar nombre del hospital): _____

Yo (indicar nombre del paciente, _____ **con DNI** _____ **siendo conocedor de las implicaciones que ello conlleva,** anulo el consentimiento prestado en fecha _____y no deseo proseguir con el tratamiento de mi enfermedad según el protocolo ofrecido. Así doy por finalizada mi participación en él a fecha de ___

Firma.:

En _____, a _____