

INTRODUCTION

Although the incidence of aggressive hematologic malignancies like acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and intermediate- and high-grade non-Hodgkin lymphomas is low, these potentially curable diseases frequently require intensive care unit (ICU) management at presentation to prevent early mortality and achieve disease remission. Patients with hematologic malignancies account for approximately 2% of all ICU admissions (**Hampshire *et al.*, 2009**).

Approximately 7% of patients with hematologic malignancies admitted to the hospital will become critically ill (**Gordon *et al.*, 2005**).

The most frequently reported indications for ICU admission in patients with hematologic malignancies are respiratory failure (26% to 91%), severe sepsis (8% to 64%), neurologic impairment (14% to 23%), and acute renal failure (14% to 23%). For all critically ill patients with hematologic malignancies, ICU mortality, in hospital mortality and 6-month mortality rates are 23% to 62%, 54% to 82%, and 66% to 83%, respectively (**Hampshire *et al.*, 2009**).

Risk factors for death in the ICU include high disease severity score, vasopressor use, leukopenia, increasing number of organ failures, and acute renal failure. Notably, mechanical ventilation has not been consistently associated with increased risk of death in this patient population, and some studies suggest improved outcomes with early endotracheal intubation (**Depuydt *et al.*, 2004**).

In addition, survival in patients with hematologic malignancies admitted to the ICU after chemotherapy alone versus hematopoietic stem cell transplant (HSCT) are not different, suggesting that critically ill HSCT patients should be treated aggressively on ICU admission. In fact, when matched for severity of acute illness upon ICU admission, survival of patients with hematologic malignancies and nononcologic patients appears to be similar (**Irwin *et al.*, 2011**).

AIM OF THE WORK

In this review, we will discuss the general strategy of ICU management of patients with hematological malignancies which will add to better understanding the nature of the disease and dealing with its complications & treatment related problems in such cases. This will help for better management of such cases and this may improve their prognosis.

BONE MARROW AND PHYSIOLOGY OF BLOOD FORMATION

Bone marrow is one of the biggest organs in the human body. Its main function is hematopoiesis providing the circulating blood with optimal supply of platelets, leukocytes and erythrocytes for coagulation, immunity and oxygen transport. Histologically, bone marrow consists of cellular components, i.e. hematopoietic and fat cells, and supporting structures, i.e. osseous trabecule, reticular-adventitial cells, and vascular, lymphatic and nervous structures. With regard to physiology, bone marrow occurs in two forms: red marrow – hematopoietically active, and yellow marrow – inactive. The red bone marrow takes its name due to a large number of erythropoietic cells, whereas yellow bone marrow – due to predominance of fat cells. Moreover, the vascular net in the red bone marrow is much thicker than in the yellow bone marrow (*Agata and Magdalena, 2012*).

Bone marrow is the flexible tissue found in the interior of bones. In humans, red blood cells are produced in the heads of long bones, in a process known as hematopoiesis. On average, bone marrow constitutes 4% of the total body mass of humans; in an adult weighing 65 kilograms & bone marrow

accounts for approximately 2.6 kilograms. The hematopoietic compartment of bone marrow produces approximately 500 billion blood cells per day, which use the bone marrow vasculature as a conduit to the body's systemic circulation (*Gordana et al., 2010*).

All blood cells are formed in the bone marrow and they arise from a type of cell called the hematopoietic stem cell (HSC). These special cells are capable of maintaining their numbers by self renewal and are capable of forming any of the numerous blood cell types. During the early stages of life, this process takes place in the yolk sac from whence it shifts to the liver and spleen during the third month of gestation. After the seventh month, the process shifts to the bone marrow (*Richard et al., 2009*).

The Two Pathways of Blood Cell Formation

An HSC can enter one of two pathways (**Fig1.**); the lymphoid pathway or the myeloid pathway to form a common lymphoid progenitor cell or a common myeloid progenitor cells, respectively. If it forms the lymphoid progenitor, it can become either a B progenitor or T progenitor. The B progenitor forms a mature B cell, while the T progenitor forms a thymocyte which leaves the bone marrow and enters the

thymus, where it differentiates to form a mature T cell (helper or cytotoxic).

If the HSC becomes a myeloid progenitor, it can become a granulocyte-monocyte progenitor, which forms a monocyte (which further differentiates into a macrophage) or a neutrophil (and probably dendritic cells).

- Eosinophil progenitor, which forms an eosinophil
- Basophil progenitor, which forms the basophil (and very likely, mast cell)
- Megakaryocyte, which forms platelets
- Erythroid progenitor, which form erythrocytes (RBCs)

(Richard et al., 2009)

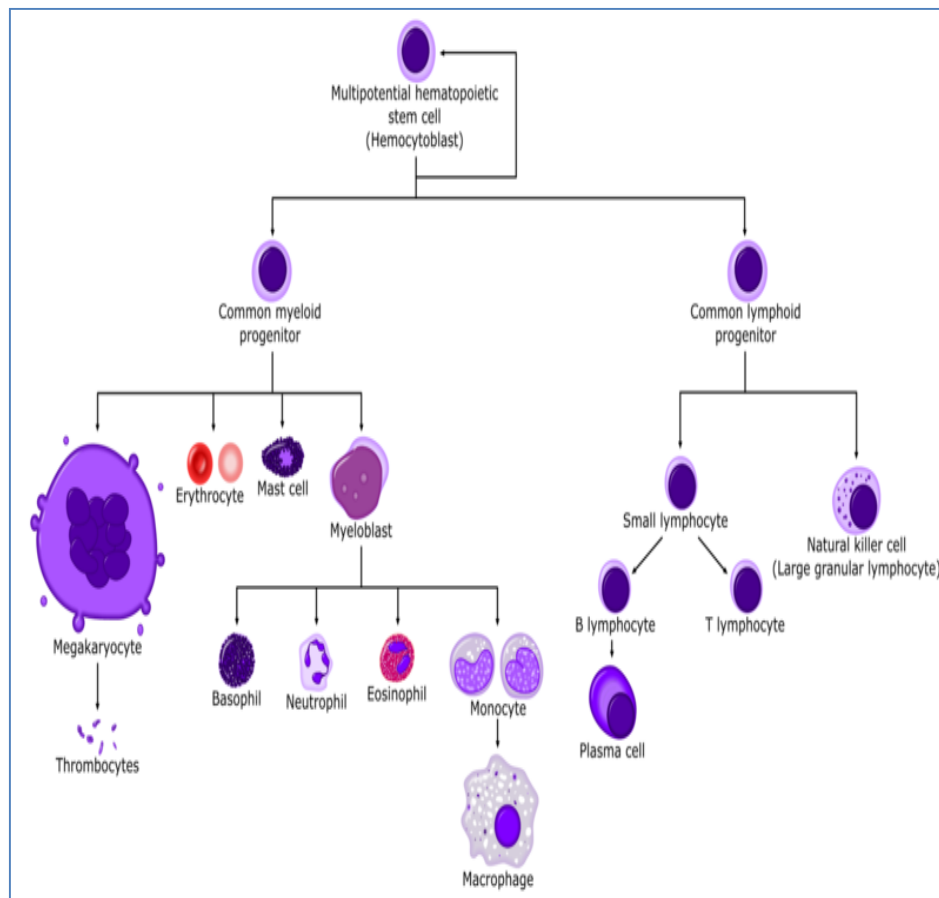


Fig. (1): (Pathway of hematopoietic stem cell)
(Lodish and Harvey, 2003).

Bone marrow microenvironment contains stem cells and other cells that are supported by hematopoietic and mesenchymal stem cells (MSCs). These cells can differentiate into several cell lineages. Osteoclasts and osteoblasts play important role in microenvironment destruction and construction (Abroun *et al.*, 2010).

Hematopoiesis Process

Hematopoiesis is a very carefully regulated process. It is regulated by complex mechanisms that affect all of the individual cell types. These regulatory mechanisms ensure steady-state levels of the various blood cell; yet they have enough flexibility to meet excessive demands of blood cells in case of hemorrhage or infections. Regulation is accomplished in various ways, including,

- Control of the levels and types of cytokines produced by bone marrow stromal cells
- Production of cytokines with hematopoietic activity by other cell types, such as activated T cells and macrophages
- Regulation of the expression of receptors for hematopoietically-active cytokines in stem cells and progenitor cells
- Removal of some cells by the controlled induction of cell death (apoptosis or programmed cell death)
- A failure in one or a combination of these regulatory mechanisms can have serious consequences

(Richard et al., 2009)

White Blood Cells

Normally, human blood contains 4000 to 11, 000 white blood cells per microliter (**Table 1**). Of these, the granulocytes (polymorphonuclear leukocytes, PMNs) are the most numerous. Young granulocytes have horseshoe-shaped nuclei that become multilobed as the cells grow older (**Figure 2**). Most of them contain neutrophilic granules (neutrophils), but a few contain granules that stain with acidic dyes (eosinophils), and some have basophilic granules (basophils). The other two cell types found normally in peripheral blood are lymphocytes, which have large round nuclei and scanty cytoplasm, and monocytes, which have abundant agranular cytoplasm and kidney-shaped nuclei (**Figure 2**). Acting together, these cells provide the body with powerful defenses against tumors and viral, bacterial, and parasitic infections (*Barrett et al., 2010*).

Table (1): Normal Values for the Cellular Elements in Human Blood (*Barrett et al., 2010*).

Cell	Cells/ L(average)	Normal Range	Percentage of Total White Cells
*Total WBCs	9000	4000–11, 000...	
-Granulocytes:			
Neutrophils	5400	3000–6000	50–70
Eosinophils	275	150–300	1–4
Basophils	35	0–100 0.4	
- Lymphocytes	2750	1500–4000	20–40
- Monocytes	540	300–600	2–8
*Erythrocytes			
Females	4.8 x 10 ⁶		
Males	5.4 x 10 ⁶		
*Platelets	300, 000	200, 000–500, 000...	

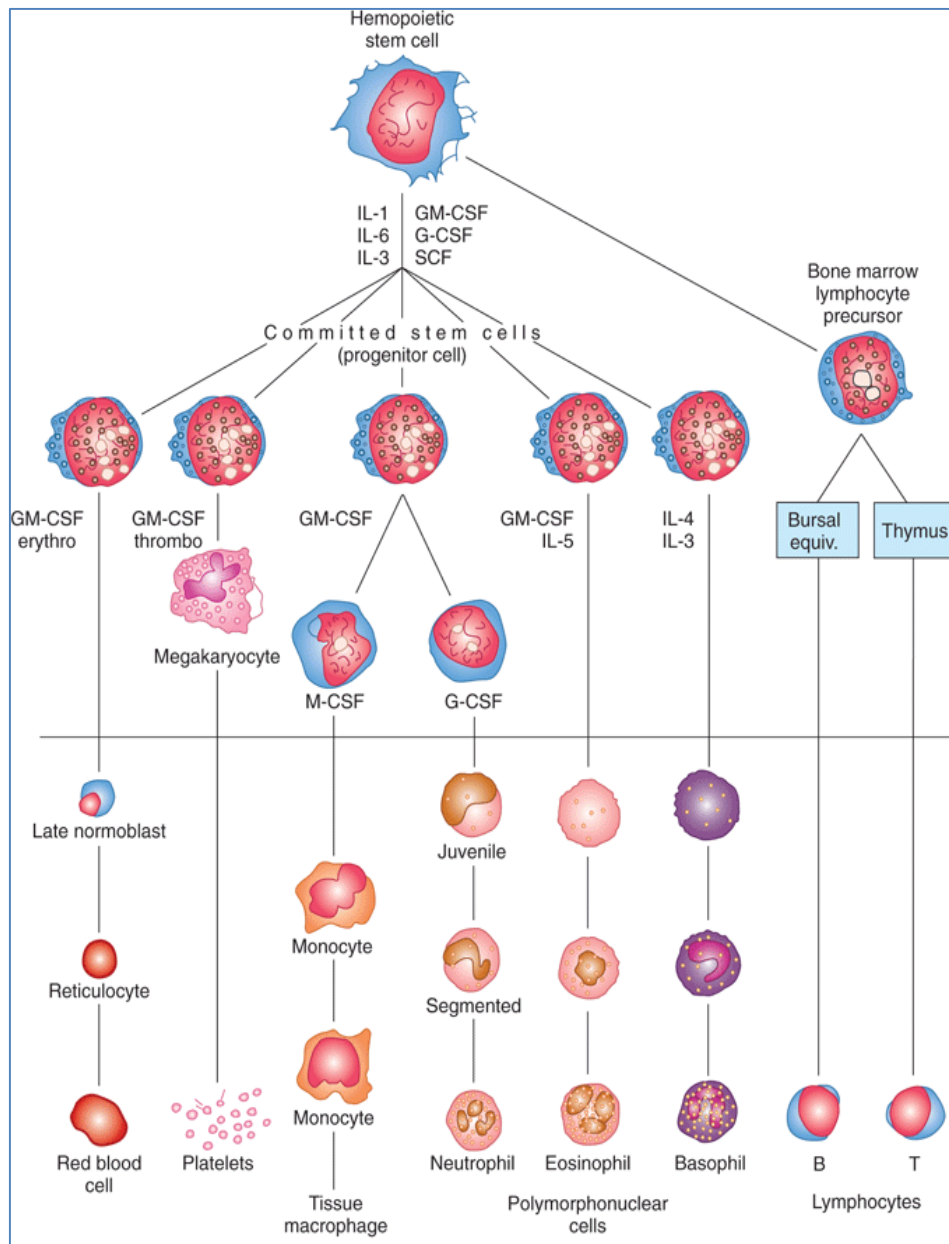


Fig. (2): Cellular elements of human blood
(Barrett et al., 2010).

Platelets

Platelets are small, granulated bodies that aggregate at sites of vascular injury. They lack nuclei and are 2–4 μm in diameter (**Figure 2**). There are about 300,000/ L of circulating blood, and they normally have a half-life of about 4 d. The megakaryocytes, giant cells in the bone marrow, form platelets by pinching off bits of cytoplasm and extruding them into the circulation. Between 60% and 75% of the platelets that have been extruded from the bone marrow are in the circulating blood, and the remainder are mostly in the spleen. Splenectomy causes an increase in the platelet count (thrombocytosis) (*Barrett et al., 2010*).

Red Blood Cells

The red blood cells (erythrocytes) carry hemoglobin in the circulation. They are biconcave disks that are manufactured in the bone marrow. In mammals, they lose their nuclei before entering the circulation. In humans, they survive in the circulation for an average of 120 days. The average normal red blood cell count is 5.4 million/ L in men and 4.8 million/ L in women. Each human red blood cell is about 7.5 μm in diameter and 2 μm thick, and each contains approximately 29 pg of hemoglobin (**Table 2**). There are thus about 3×10^{13} red blood

cells and about 900 g of hemoglobin in the circulating blood of an adult man (*Barrett et al., 2010*).

Table (2): Characteristics of Human Red Cells (*Barrett et al., 2010*).

	Male	Female
Hematocrit (Hct) (%)	47	42
Red blood cells (RBC) (10 ⁶ / L)	5.4	4.8
Hemoglobin (Hb) (g/dL)	16	14
Mean corpuscular volume (MCV) (fL)	87	87
Mean corpuscular hemoglobin (MCH) (pg)	29	29
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	34	34
Mean cell diameter (MCD) (m) = Mean diameter of 500 cells in smear	7.5	7.5

Cells with MCVs > 95 fL are called macrocytes; cells with MCVs < 80 fL are called microcytes; cells with MCHs < 25g/dL are called hypochromic.

HEMATOLOGICAL MALIGNANCIES PATHOPHYSIOLOGY AND TREATMENT

Definition:

Hematological malignancies are group of diseases resulting from the neoplastic proliferation of hemopoietic or lymphoid cells. It results from mutation of a single stem cell, the progeny of which forms a clone of leukemic cells. Usually there is a series of genetic alterations rather than a single event. Genetic events contributing to malignant transformation include inappropriate expression of oncogenes and loss of function of tumor suppressor genes (*Bain, 2010*).

Overview of hematological malignancies:-

The most types of hematological malignancies are classified into:

- A) Myelodysplastic syndrome (MDS)
- B) Acute leukemia
- C) Chronic myeloid leukemia
- D) Chronic lymphocytic leukemia
- E) Plasma cell neoplasms
- F) Myeloproliferative disorders

A) MYELOYDYLASTIC SYNDROME (MDS)

MDS are a group of hematological disorders that occur mainly in older persons and are characterized by peripheral cytopenias and an increasing risk of progression into acute myeloid leukemia (AML). The impressive heterogeneity of the natural history of MDS, ranging from indolent conditions to forms rapidly progressing to leukemia, complicates clinical decision making regarding therapy (*Malcovati et al., 2006*).

MDS may either be apparently primary or may be secondary to cytotoxic chemotherapy, irradiation or other environmental toxins. There is a discrepancy between a normocellular bone marrow (BM) and peripheral blood (PB) cytopenia except in 10% of cases the marrow is hypocellular (*Malcovati et al., 2006*).

WHO (2008) classification of myelodysplastic syndrome (MDS):

- Refractory cytopenia with unilineage dysplasia
 - Refractory anemia
 - Refractory neutropenia
 - Refractory thrombocytopenia
 - Refractory anemia with ring sideroblasts
 - Refractory cytopenia with multilineage dysplasia
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