Introduction

The balance between cell death and cell viability is important in tissue homeostasis. Abnormalities in the control of programmed cell death (apoptosis) play an important role in tumorigenesis ***(Tazzari et al., 2008).***

The evolutionarily conserved multi-step apoptosis cascade is regulated by proteins that promote or inhibit apoptotic cell death ***(Jakubowska et al., 2007).***

The inhibitor of apoptosis survivin is a member of the inhibitor of apoptosis protein (IAP) family that suppresses apoptosis or programmed cell death and regulates cell division and thereby integrates apoptosis and cell division ***(Badran et al., 2004).***

The survivin protein shuttles between the nucleus and the cytoplasm, where it effectively inhibits apoptosis, most likely bybinding to second mitochondrial activator of caspase (Smac) ***(Song et al., 2003).***

One of the clinically significant features of survivin is its differential distribution in many cancers compared with its limited expression in normal terminally differentiated tissues ***(Johnson and Howerth, 2004).***

Over expression of several IAPs has been detected in various hematological malignancies, including acute leukemias,

myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), and many types of lymphoid malignancies, such as chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL). Many publications revealed significant correlation between a high level of IAPs, especially of XIAP and survivin, and tumor progression contributing to leukemogenesis due to deregulated apoptosis ***(Wrzesień-Kuś et al., 2004; Troeger et al., 2007).***

The expression of survivin maybe a general feature of cancer and survivin alone or with other antiapoptosis genes such as Bcl-2 may extend the viability of transformed cells and regulate their susceptibility / resistance to apoptosis-based therapy. For this reason survivin may provide an ideal therapeutic target for its selective expression in neoplasia ***(Ambrosini et al., 1997).***

Various strategies have been developed to target IAPs for the rapeutic purposes in leukemia and lymphoma cells, including small-molecule inhibitors and antisense oligonucleotides ***(Fulda, 2009).***

Aim of the Work

The aim of the present study is to assess expression of survivin on malignant myeloid blast cells and its correlation with clinical outcome, disease progression, overall survival, disease free survival and relapse rate and the other prognostic factors in adult patients with acute myeloid leukemia.

Chapter (I): Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignant stem cell disorder characterized by a disruption in hematopoiesis resulting in accumulation of immature or blast cells in the bone marrow and the peripheral blood ***(Zander et al., 2008).***

This leads to bone marrow failure, severe cytopenias and death if left untreated. The incidence of AML increases with age, with the majority of patients older than age 60. Elderly patients with AML have a particularly poor prognosis ***(Christine and James, 2011).***

Diagnosis:

Patients typically present with symptoms of anemia. If bleeding is prominent, it is crucial to immediately rule in/rule out acute promyelocytic leukemia (APL). Depends on demonstration that the marrow or blood has >20% blasts of myeloid lineage. Blast lineage is assessed by multi parameter flow cytometry showing myeloid lineage antigens include CD33, CD13, CD117 (CKIT), CD14, CD64 CD41, and glycophorin A on myeloid blasts ***(Estey, 2012).***

The earlier French-American-British (FAB) classification of AML is mainly based on morphology and cytochemistry,

and it classifies AML into eight groups, namely AML-M0 to -M7 (Table 1).

Table (1): AML-M0 to -M7.

M0	Minimally differentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia, without maturation
M2	Acute myeloblastic leukemia, with granulocytic maturation
M3	Acute Promyelocytic Leukemia (APL)
M4	Acute Myelomonocytic Leukemia, And Acute Myelomonocytic with Eosinophilia (M4eo)
M5	Acute Monoblastic Leukemia (M5a) and Acute Monocytic Leukemia (M5b)
M6	Acute erythroid leukemias
M7	Acute megakaryoblastic leukemia

(Lyu et al., 2013)

WHO Classification

The recent WHO classification reflects the fact that an increasing number of acute leukemias can be categorized based upon their underlying cytogenetic or molecular genetic abnormalities, and that these genetic changes form clinico-pathologic genetic entities (Table 2).

Table (2): Acute myeloid leukemia and related precursor neoplasms, and acute leukemias of ambiguous lineage.

Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21) (q22;q22); RUNX1-RUNX1T1
AML with inv (16) (p13.1q22) or t(16;16) (p13.1; q22); CBFB-MYH11
APL with t(15;17) (q22;q12); PML-RARA
AML with t(9;11) (p22;q23); MLLT3-MLL
AML with t(6;9) (p23;q34); DEK-NUP214
AML with inv(3) (q21q26.2) or t(3;3) (q21;q26.2); RPN1-EVI1
AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified (NOS)
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemia
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)
Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL
Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged
Mixed phenotype acute leukemia, B/myeloid, NOS
Mixed phenotype acute leukemia, T/myeloid, NOS
Provisional entity: Natural killer (NK)–cell lymphoblastic leukemia/lymphoma

(Löwenberg et al., 2010)

The subgroup "AML with recurrent genetic abnormalities" comprises several primary AML entities. "AML with t(8;21) (q22;q22); *RUNX1-RUNX1T1*" and "AML with inv (16) (p13.1q22) or t(16;16) (p13.1;q22); *CBFB-MYH11*" are considered as AML regardless of bone marrow blast counts. In "APL with t(15;17) (q22;q12); *PML-RARA*," *RARA* translocations with other partner genes are recognized separately. The former category "AML with 11q23 (*MLL*) abnormalities" was redefined in that "AML with t(9;11) (p22;q23); *MLLT3-MLL*" is now a unique entity; balanced translocations other than that involving *MLLT3* should be specified in the diagnosis ***(Löwenberg et al., 2010).***

Three new cytogenetically defined entities were incorporated: "AML with t(6;9) (p23;q34); *DEK-NUP214*"; "AML with inv(3) (q21q26.2) or t(3;3) (q21;q26.2); *RPN1-EVI1*"; and "AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*," a rare leukemia most commonly occurring in infants. Two new provisional entities defined by the presence of gene mutations were added, "AML with mutated *NPM1* [nucleophosmin (nucleolar phosphoprotein B23, numatrin)], "and "AML with mutated *CEBPA* [CCAAT / enhancer binding protein (C/EBP), alpha]." There is growing evidence that these 2 gene mutations represent primary genetic lesions (so-called class II mutations) that impair hematopoietic differentiation ***(Kelly and Gilliland, 2002).***

The former subgroup termed “AML with multiline age dysplasia” is now designated “AML with myelodysplasia-related changes.” Dysplasia in 50% or more of cells, in 2 or more hematopoietic cell lineages, was the diagnostic criterion for the former subset AMLs are now categorized as “AML with myelodysplasia-related changes” if (1) they have a previous history of myelodysplastic syndrome (MDS) or myelodysplastic / myeloproliferative neoplasm (MDS/MPN) and evolve to AML with a marrow or blood blast count of 20% or more; (2) they have a myelodysplasia-related cytogenetic abnormality; or (3) if 50% or more of cells in 2 or more myeloid lineages are dysplastic ***(Wandt et al.,2008).***

Therapy-related myeloid neoplasms (t-AML/t-MDS and t-AML/ t-MDS/MPN) remain as a distinct subgroup in the AML classification. Although cases may be designated as t-AML, or as t-MDS or t-MDS/MPN depending on the blast count, it is useful to think of them as a single biologic disease with similar genetic features, so that the designation as t-AML/t-MDS is appropriate as well ***(Singh et al., 2007).***

Most patients who develop therapy-related myeloid neoplasms have received alkylating agents and/or radiation as well as topoisomerase II inhibitors, so that a division according to the type of therapy is usually not practical and is no longer recommended. It has been argued that 90% of patients with therapy-related neoplasms have cytogenetic abnormalities

identical to those observed in AML with myelodysplasia-related features or in AML with recurrent cytogenetic abnormalities, therefore such cases would be more appropriately classified in those categories rather than in a separate, therapy-related category ***(Vardiman et al., 2009).***

However, except for some patients with t-AML associated with inv(16) (p13.1q22), t(16;16) (p13.1;q22) or t(15;17) (q22;q12), patients with therapy-related myeloid neoplasms have a significantly worse outcome than do their de novo counterparts with the same genetic abnormalities, suggesting that there are biologic differences ***(Bloomfield et al., 2002).***

AML, Not Otherwise Specified (NOS) Despite at tempts to utilize a biologic-based classification of AML to the greatest extent possible, the 2008 WHO classification has included 11 subtypes of AML, not otherwise specified (NOS) ***(Vardiman et al.,2009).***

A lineage-based system is used to subclassify those cases of AML that lack any specific AML-defining biologic characteristic. Consequently, the AML, NOS category is reserved for cases that fulfill general criteria for AML but *lack:* a) an AML recurrent cytogenetic or molecular abnormality, b) a link to prior chemotherapy, c) multilineage dysplasia involving the majority of cells, d) MDS-type cytogenetic abnormalities, e) an association

with Down syndrome, or f) a history of MDS or MDS/MPN ***(Foukar et al., 2011).***

Although up to 1/3 of AML cases currently fall into AML, NOS, it is likely that this proportion will steadily decline as more biologic entities are defined by molecular genetic studies ***(Haferlach et al., 2009).***

Myeloid sarcomas are rare extramedullary solid tumors composed of immature cells derived from a myeloid hematopoietic lineage. They are also known as chloromas, myeloblastomas, myelocytomas, chloroleukemia and granulocytic sarcomas and are associated with acute myeloid leukemia (AML) and blastic transformation of chronic myeloproliferative disorders (chronic myeloid leukemia, polycythemia vera and primary myelofibrosis) and myelodysplastic syndromes. They may manifest without any initial compromise of the bone marrow ***(Campidellic et al., 2009).***

Myeloid sarcomas are associated with AML in 2-8% of the cases, especially in situations of cytogenetic abnormalities such as t(8;22), inv(16) and 11q23. They may be presented simultaneously with AML, as a form of extramedullary disease in recurrence, or may be separate findings that precede an increase in the number of myeloblasts in the bone marrow by some weeks or months. In such situations, blastic infiltration of the bone marrow is not seen ***(Beatriz, 2013).***

Myeloid leukemia associated with Down syndrome (MLADS) in the pediatric age group is overwhelmingly megakaryoblastic in nature, as is transient abnormal myelopoiesis (TAM) described further in “Down Syndrome-Associated AML and Transient Abnormal Myelopoiesis,”. Interestingly, both processes harbor acquired mutations in *GATA1*, a gene on the short arm of the X chromosome that encodes a transcription factor. *GATA1* mutations seem to be surprisingly specific for these settings. The GATA family of proteins contain zinc finger domains that bind specific DNA sequences. In fact, the name “GATA” is derived from the key portion of the sequence recognized: G-A-T-A ***(Foukar et al., 2011).***

MDS related to Down syndrome is biologically identical to Down-related AML; therefore they are considered as a single entity, myeloid leukemia associated with Down syndrome, in the classification ***(Vardiman et al., 2009).***

The neoplasm referred to in the WHO 3rd edition as “blastic NK-cell lymphoma” or in the literature as “agranular CD4_/ CD56_ hematodermic neoplasm” is now known to be in virtually all cases a tumor that is derived from precursors of a specialized subset of dendritic cells, plasmacytoid dendritic cells, and hence is a myeloid-related neoplasm ***(Pilichowska et al., 2007).***

It is a clinically aggressive neoplasm that is usually characterized at its onset by solitary or multiple skin lesions, often with associated regional lymphadenopathy. Many cases will ultimately progress to involve the PB and BM as well. The blasts in such cases do not express myeloperoxidase or nonspecific esterase, and they are characterized by the expression of CD4, CD43, CD56, CD123, BDCA-2/CD303, TCL1, and CLA; CD7 and CD33 are not uncommonly expressed as well, and TdT is expressed in approximately 30% of cases. There is no expression of CD34 or CD117 ***(Pilichowska et al., 2007).***

Acute Leukemia of Ambiguous Lineage

Acute leukemia of ambiguous lineage (ALAL) is a rare subtype of acute leukemias that does not show any clear evidence of differentiation along a single lineage ***(Kim et al., 2013).***

In some cases, no lineage specific antigens are present, whereas in others the blasts express antigens of more than one lineage to such a degree that it is not possible to assign the leukemia to a specific lineage-related category ***(Vardiman et al., 2009).***

Prognosis

Prognostic factors may be subdivided into those related to patient characteristics and general health condition and those related to characteristics particular to the AML clone.

Patient-Related Factors

Increasing age is an adverse prognostic factor. Even after accounting for risk factors, such as cytogenetics, molecular genetics, type of AML (ie, de novo AML; AML with previous history of MDS or MDS/MPN; therapy-related AML), and performance status, older patients have worse outcomes than younger patients, suggesting the effect of unknown age-related factors. Nonetheless, calendar age alone should not be a reason for not offering potentially curative therapy to an older patient, because age is not the most important prognostic factor for either TRM or resistance to therapy ***(Juliusson et al., 2009).***

AML-Related Factors

AML-related prognostic factors includes white blood count (WBC), existence of prior MDS, previous cytotoxic therapy for another disorder, and cytogenetic and molecular genetic changes in the leukemic cells at diagnosis ***(Löwenberg et al., 2010).***

The European Leukemia Network (ELN) categorizes patients into one of four groups depending on cytogenetic and molecular genetic (NPM1, FLT3, and CEBPA) status (Table 3).

Table (3): European Leukemia Net (ELN) Prognostic System.

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD (NK) Mutated CEBPA (NK)
Intermediate I	Mutated NPM1 and FLT3-ITD (NK) Wild-type NPM1 and FLT3-ITD (NK) Wild-type NPM1 without FLT3-ITD (NK)
Intermediate II	t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities other than favorable or adverse{
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged 25 or del(5q); 27; abnl(17p); complex karyotype

(Estey, 2012)

Management of Younger Adults: 18 to 60 years

Induction therapy

Three days of an anthracycline (eg, daunorubicin, at least 60 mg/m^2 , idarubicin, 10-12 mg/m^2, or the anthracenedione mitoxantrone, 10-12 mg/m^2) and 7 days of cytarabine (100-200 mg/m^2 continuous IV) ("3 + 7") currently remains the standard for induction therapy. With such regimens, CR is achieved in 60% to 80% of younger adults. No other intervention has been convincingly shown to be better ***(Sekeres et al., 2009).***

Post Remission Therapy According to Cytogenetic and Molecular Genetic Risk

Favorable-risk AML: Postremission therapy with repetitive cycles of HiDAC (3 g/m^2 per q12h on days 1, 3, and 5) is considered a reasonable choice for younger adult patients with CBF AML, and also for AML with mutated *NPM1* without *FLT3*-ITD and with mutated *CEBPA* ***(Schlenk et al., 2008).***

For CBF AML, retrospective studies by CALGB suggest that 3 or more cycles of HiDAC (cumulative dose: 54-72 g/m^2) are superior to only one cycle (18 g/m^2). No advantage has been shown for autologous or allogeneic HSCT in frontline treatment ***(Koreth et al., 2009).***

Nonetheless, there are subsets of CBF AML that do rather poorly [eg, t(8;21) with high WBCs, CBF AML with *KIT* mutations or molecular disease persistence]; allogeneic HSCT may be considered in these patients ***(Krauter et al., 2008).***

Intermediate-risk AML

For the remaining patients with intermediate-I and those with intermediate-II karyotypes, repetitive cycles of HiDAC (3-4 cycles; 3 g/m^2 per q12h on days 1, 3, and 5) are currently widely used by many cooperative groups; however, outcome for most of the subsets remains unsatisfactory ***(Löwenberg et al., 2010).***