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Prognosis and Survival in Acute Myelogenous Leukemia

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1. Introduction

Progress in understanding the prognosis and survival in acute myelogenous leukemia (AML) has been dramatic over the last few decades. Traditionally, clinical risk factors such as age and performance status have been the main prognostic factors in AML. However, recent advances in cytogenetic studies and molecular markers in AML have revolutionized our approach to this disease. These have changed our understanding of AML as a heterogeneous group of diseases rather than a single disease, provided greater insight not only in understanding disease biology but also into predicting response to therapy and helped in the development of risk stratification-based treatment approach.

In 2010, there are about 12,330 new cases in the United States which represent about 0.8% and 29% of all new cancer and leukemia cases respectively. With about 8,950 estimated deaths related to AML, this represents about 1.6% of cancer related deaths in 2010. (American Cancer Society, 2010)

Although there has been some improvement in survival for AML patients over the last few decades, mainly in younger age groups as shown in figure 1, AML long term survival is still a big challenge. In the United States, data from Surveillance Epidemiology and End Results (SEER) dataset for 2001 to 2007 showed 5-year overall survival (OS) of 22.6% for all AML patients. There is still a lot to be done especially in the oldest age group (>65 years), that is showing a dismal 5-year OS of less than 5%, See Figure 2. This is of particular concern as more than half of the patients diagnosed in 2000-2004 were over 65 years old. (Howlader et al., 2011).

2. Clinical prognostic factors

2.1 Age

AML is seen more commonly in the elderly with median age at diagnosis of 66 with incidence increases dramatically after age of 55, See figure 3. Data from SEER (see figure 2) as well as from major studies of the largest cooperative groups including the Medical Research Council (MRC), the Southwest Oncology Group/Eastern Cooperative Oncology Group (SWOG/ECOG), AML cooperative group (AMLCG) and the Cancer and Leukemia Group B (CALGB) that included elderly patients have shown consistently worse outcome in this patient population, See figure 4. (Slovak et al., 2000; Byrd et al., 2002; Schoch et al., 2004a; Grimwade & Hill., 2009)

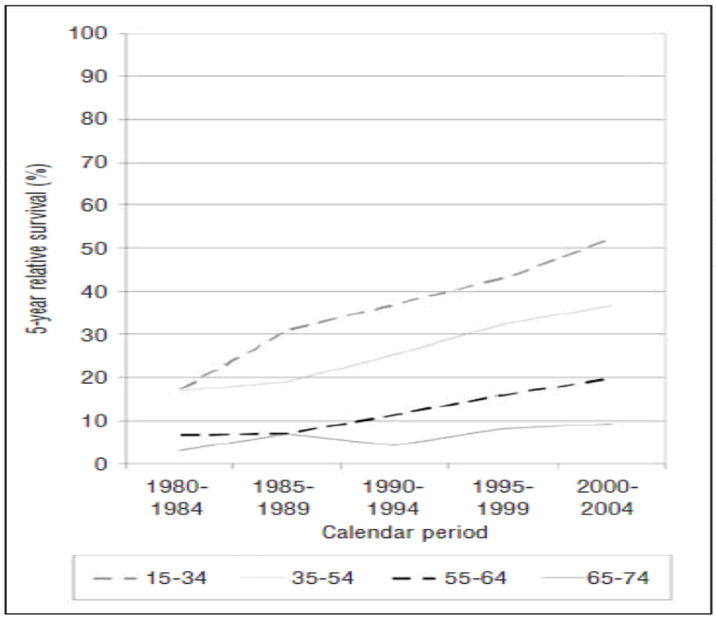


Fig. 1. Period estimates of 5-year relative survival of patients with AML by major age groups in defined calendar periods from 1980-1984 to 2000-2004. (Pulte et al., 2008).

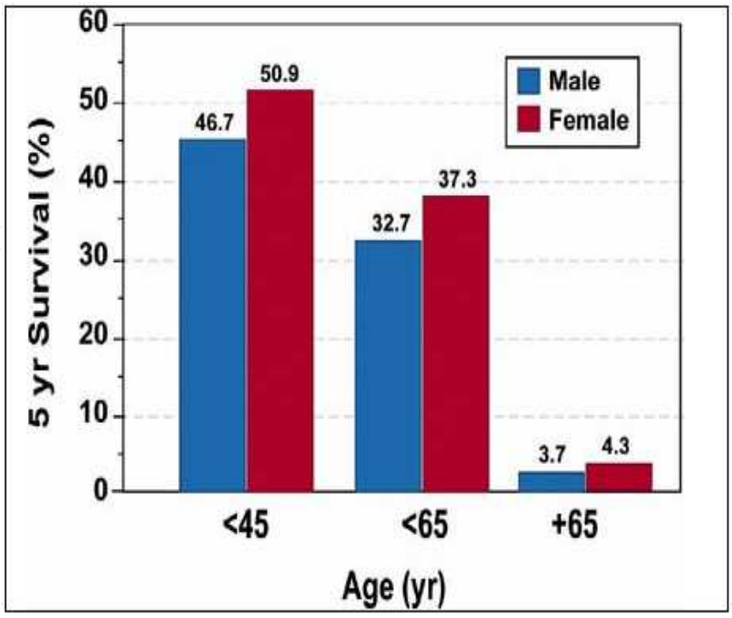


Fig. 2. Age and sex-associated with 5-year relative survival in patients with AML in the United States, 1996–2003 (From SEER cancer statistics, National Cancer Institute, 2007.)

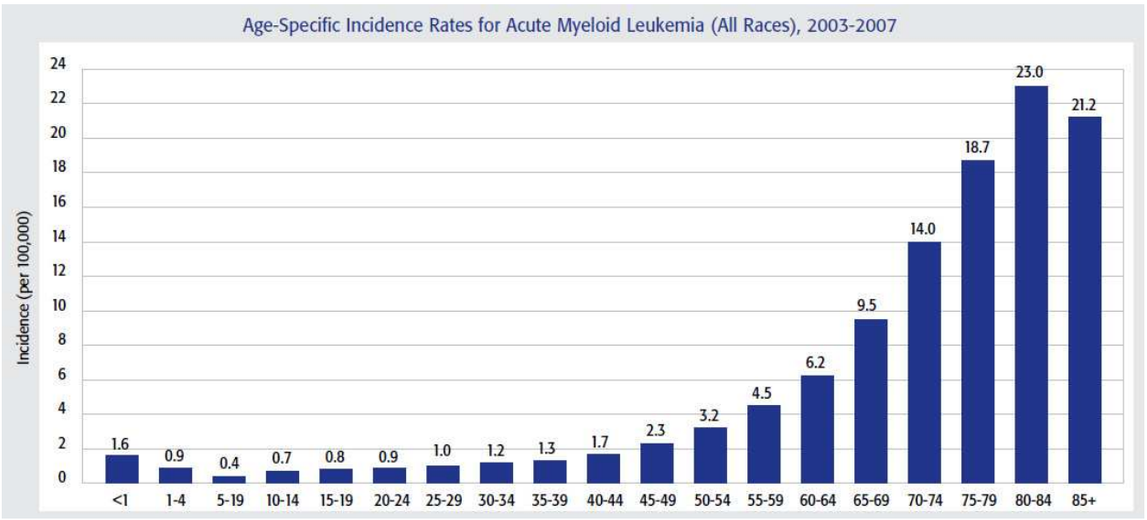
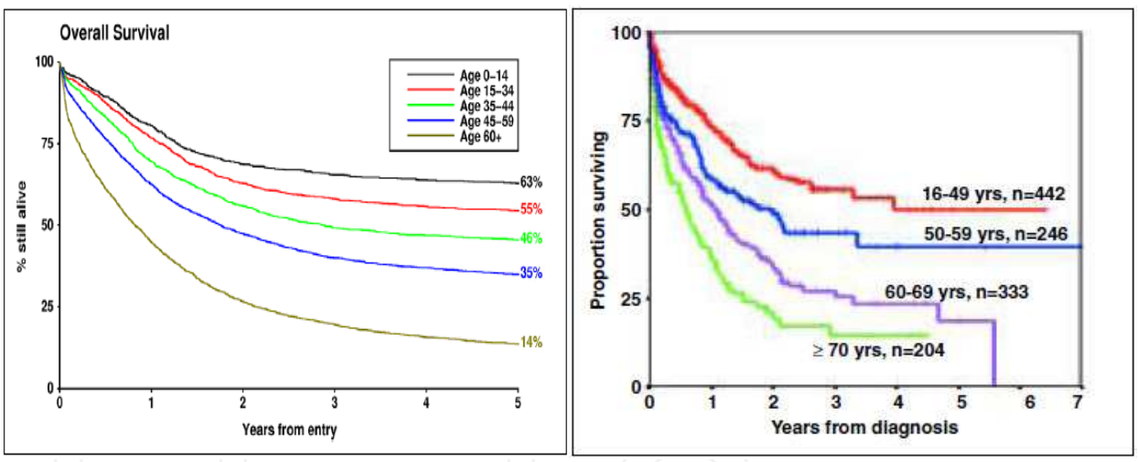


Fig. 3. Age-Specific incidence rates for AML from 2003 to 2007. (Altekruse et al., 2010).



(a) (b)

Fig. 4. Survival curves according to age groups. a: Patients treated in MRC AML trials (AML10, 11, 12, 14 and 15) (Smith et al. , 2011). b: Patients treated in AMLCG trials (AMLCG 1992, AMLCG 1999 and AMLCG APL trials) (Schoch et al., 2004a)

The worse outcome in elderly population is related to two components: resistance to treatment and treatment-related death. It is believed that most of treatment failure in elderly is related to the first component. This is mainly related to distinct biological and clinical features such as higher percentage of poor cytogentics, higher incidence of multidrug resistance protein (MDR) and preceding hematological disease, all of which are associated independently with worse prognosis in AML. (Lieth et al., 1997; Estey 2007). For example, in retrospective analysis from five SWOG clinical trials more than 50% of patients >75 years old had poor cytogenetics which translated into complete remission (CR) rate of 33%, See figure 5, table 1. (Appelbaum et al., 2006a)

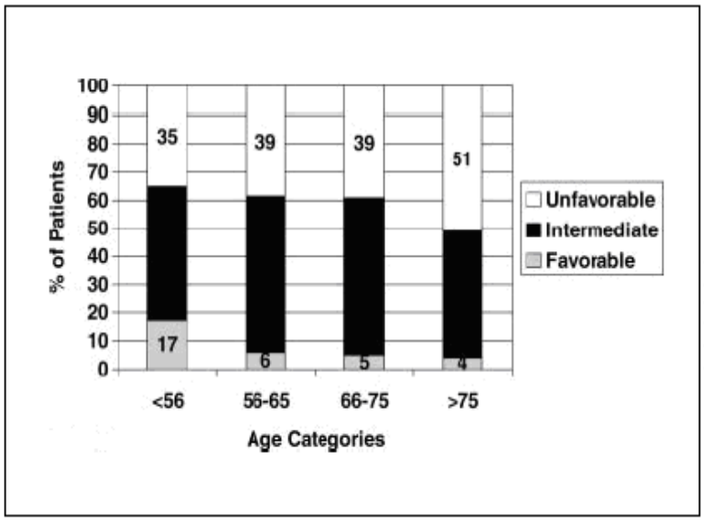


Fig. 5. Percentage of patients in the different cytogenetic risk groups by age category in five SWOG clinical trials (Appelbaum et al., 2006a).

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	368	246	274	80
Response, no. (%)				
CR	235 (64)	113 (46)	108 (39)	26 (33)
Resistant disease	99 (27)	91 (37)	101 (37)	29 (36)
Median overall survival, no. (95% CI)	18.8 (14.9-22.6)	9.0 (8.1-10.2)	6.9 (5.4-7.7)	3.5 (1.4-6.1)
No. patients with CR	235	113	108	26
Median disease-free survival, no. (95% CI)	21.6 (15.8-25.5)	7.4 (6.5-8.8)	8.3 (6.3-10.2)	8.9 (5.8-10.8)

Table 1. CR rates in different age groups in the same patient population (Appelbaum et al., 2006a).

The second component of treatment failure is treatment-related death. This is mainly related to the worse performance status and organ function in this age group. Multiple studies have shown age along with poor performance status as very strong predictors of early post-induction mortality in AML, See table 2, Figure 6. (Appelbaum et al., 2006a; Juliusson et al., 2009).

This has motivated researchers to develop different prognostic and predictive models including clinical and laboratory variables that can help physicians deciding treatment in this challenging patient population. (Krug et al., 2010; Kantarjian et al., 2010)

Even after accounting for the above factors, elderly patients tend to have worse outcome with less CR rate and higher mortality rate. In two different reports from SWOG and AMLCG, elderly patients with favorable cytogenetic have worse outcome compared to younger patients. (Schoch et al,. 2004a; Appelbaum et al., 2006a)

The dismal prognosis in elderly population has another component which is undertreatment. While AML is more common in elderly, a large number of these patients do not receive intensive chemotherapy. This is because they are more likely to have poor

performance status and comorbidities at diagnosis and therefore less frequently judged to be fit for induction therapy. Menzin et al,. reviewed SEER data of AML in elderly patients. Among 2657 patients age > 65 years reviewed, only 30% of patients underwent intensive chemotherapy. Juliusson et al reported similar numbers from the Swedish Acute Leukemia Registry with only 45% of patients in age group 70-74 offered treatment as compared to 92% in 60-64 age group and 98% in <50 age group (Juliusson et al., 2009).

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	364	242	270	79
Early deaths* by performance status, no./no. total patients (%)				
0	3/129 (2)	8/72 (11)	9/73 (12)	2/14 (14)
1	6/180 (3)	6/112 (5)	20/126 (16)	7/40 (18)
2	1/46 (2)	6/34 (18)	16/52 (31)	7/14 (50)
3	0/9 (0)	7/24 (29)	9/19 (47)	9/11 (82)

Table 2. Mortality within 30 days of induction treatment according to age group and performance status in 5 clinical SWOG trials (Appelbaum et al., 2006a).

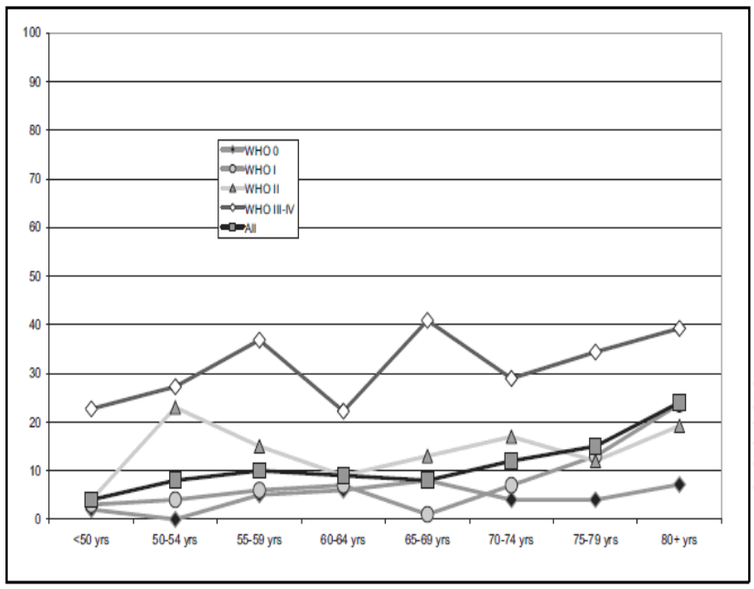


Fig. 6. Mortality within 30 days of induction treatment according to age group and performance status the Swedish acute leukemia registry (Juliusson et al., 2009).

So when interpreting data from various clinical trials we have to keep in our minds that the patient population in clinical trials includes only a subset of elderly patients with AML and survival numbers achieved could be an overestimate in this patient population. In the same report from Menzin et al including treated and untreated AML patients, patients older than 65 years had a median survival of two months with two-year OS of 6% (Menzin et al., 2002).

2.2 Performance status

Different clinical trials have consistently showed worse outcome in patients with poor performance. It is considered the strongest predictor of 30-day mortality after induction therapy, See table 2, Figure 6. (Appelbaum et al., 2006a; Juliusson et al., 2009). Poor performance usually reflects comorbidities and organ dysfunction. Assessing this parameter in elderly patients can be difficult. Acute infection or decompensation can easily change performance status and confuse our assessment of baseline performance status. Clinical trials exclude patients with poor performance status, so when reviewing data from any clinical trial we have to keep in our minds that it excludes a major part of patients who are rendered ineligible. This selection bias is more pronounced in elderly population as fit elderly are more likely to receive treatment.

2.3 Prior hematological disease

The prior diagnosis of myelodysplastic (MDS) or myeloproliferative (MPD) disease is well established as a poor prognostic factor in AML patients. While the poor survival is more associated with high prevalence of advanced age and poor cytogenetics in this patient population, it is still an independent prognostic factor after adjusting for both variables. Longer interval from onset of MDS or MPD disease to AML negatively affected outcomes in this patient population. One explanation is that a protracted history of prior hematological disease may select for higher rates of chemotherapy resistance after AML develops. Prior treatment for MDS is another poor prognostic factor in this patient population. (Bello et al., 2011).

2.4 Therapy-related AML

People exposed to cytotoxic agents are at higher risk of developing AML among other myeloid neoplasms. Therapy-related AML (t-AML) represents about 10-15% of all cases of AML (Schoch et al., 2004b). it is considered a poor prognostic factor. Goldstone et al. reported OS of 30% compared to 44% in de novo AML (Goldstone et al., 2002). In another report from Kayser et al, Outcome of patients with t-AML was significantly inferior with 4-year OS of 25.5% compared to 37.9% in de novo AML. (Kayser et al., 2011)

The risk is highest after exposure to two classes of cytotoxic agents: topoisomerase II inhibitors and alkylating agents. The current WHO classification does not subcategorize t-AML based on agents involved. This is mainly due the fact that most patients developing t-AML have been exposed to both types and it is not feasible to discriminate according to the previous therapy. (Swerdlow et al., 2008)

Each class related-AML has certain characteristics. While alkylating agents related-AML frequently is preceded by myelodysplastic phase and a long interval between exposure and development of AML (36-72 months), topoisomerase II related-AML usually presents without myelodysplastic phase and has an interval of usually 6 to 36 months. While alkyalting agents are usually associated with unbalanced cytogenetic abnormalities involving chromosome 5 and 7 as well as complex karyotype, patients with topoisomerase II inhibitors related t-AML are more likely to have balanced translocations involving MLL at 11q23, NUP98 at 11p15, RUNX1 at 21q22 and RARA at 17q21.

t-AML is commonly associated with abnormal karyotype ranging between 69 to 96%. Cytogenetic abnormalities in t-AML are the same described in de novo AML but with different frequencies. In one report, 46% of t-AML patients had unfavorable cytogenetic

profile as compared to 20% in de novo AML and only 10% had normal cytogenetics versus 40% in de novo AML. Similar distribution has been observed in other trials as well. (Schoch et al., 2004b ; Grimwade & Hill 2009; Kayser et al., 2011)
Patients with t-AML tend to be older than de novo AML patients. In one report , median age of t-AML was 57.8 years versus 53.2 years in de novo AML. (Kayser et al., 2011)
While the above factors contribute to the worse outcome seen in t-AML, inferior survival and response rate has been observed in all age and cytogenetic subgroups (Grimwade & Hill 2009; Borthakur et al., 2009), See figure 7.

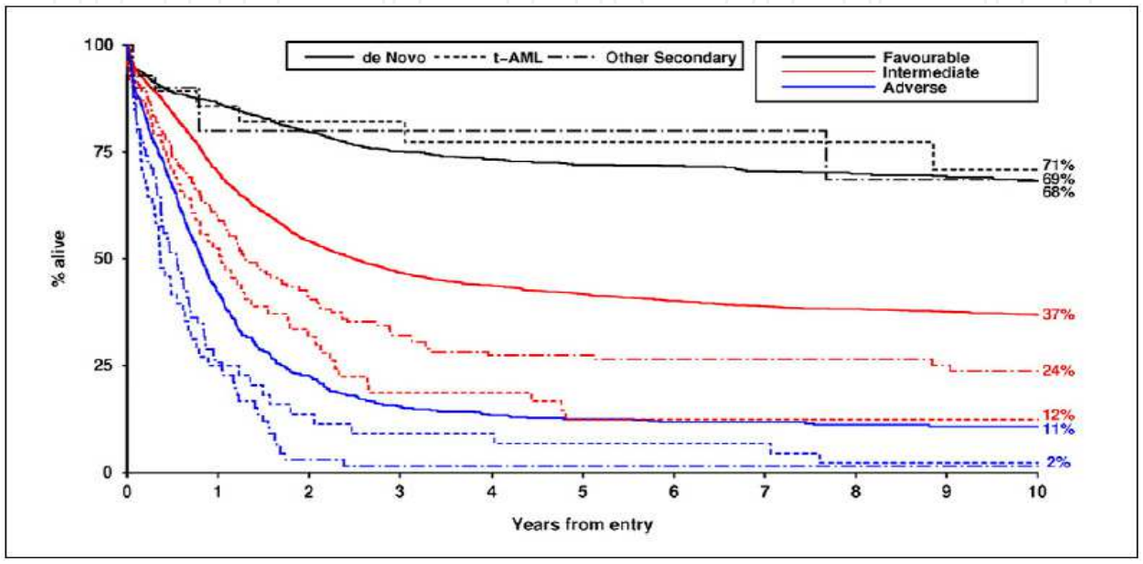


Fig. 7. Survival curves according to cytogenetics subgroups for patients treated in MRC AML trials (AML10, 11, 12, 14 and 15) with t-AML and de novo AML (Grimwade & Hill 2009).

2.5 Others

Clinical markers of high tumor burden like high LDH , high peripheral white blood cell (WBC) count and need for cytoreduction therapy are reported to be of adverse impact on prognosis. As will be discussed later in details, certain molecular abnormalities (FLT3 or KIT mutations) are more associated with high WBC count which could be the actual factor contributing to the prognosis. So much of the prognostic impact of leukocytosis may reflect the molecular abnormalities driving the proliferation. (Dalley et al., 2001; Martin et al., 2000; Burnett et al., 1999) Extramedullary involvement has been associated with worse outcome as well. (Change et al., 2004)

3. Karyotype

50 to 60 % of adult patients with de novo AML have karyotype abnormalities. Cytogenetics is the most powerful prognostic factor in AML. This has been illustrated in several analyses from small single institution studies as well as large multi-institutional trials from various research groups. Its importance has exceeded other variables by consistently showing strong prognostic value in predicting CR, risk of relapse as well as survival, See figure 7

(Grimwade & Hill 2009; Byrd et al., 2002; Slovak et al., 2000). Therefore it is the single most important factor that provides a framework for the current risk-stratified treatment approach in AML. This is clearly reflected on the current WHO classification of AML in which different groups are specified according to the cytogenetic abnormalities. (Swerdlow et al., 2008)

While there is agreement among different groups on defining the favorable cytogenetics group, there is variation on assigning the rest of karyotype abnormalities in the other two groups (i.e. intermediate and adverse). This could be related to variation in patient characteristics, treatment protocols among various trials, as well as the relatively small number of patients having a certain cytogenetic abnormalities in each trial. Table 3 is showing different cytogenetics risk groups in major cooperative groups clinical trials.

	Original MRC	SWOG/ECOG	CALGB	GIMEMA/ AML10	German AMLCG	HOVON/ SAKK	Refined MRC
Favorable	t(15;17) t(8;21) inv(16)/t(16;16)	t(15;17) t(8;21) [lacking del(9q), complex, ie, ≥ 3 unrel abn] inv(16)/t(16;16)/del(16q)	t(15;17) t(8;21) inv(16)/t(16;16)	t(15;17) t(8;21) inv(16)/t(16;16)	t(15;17) t(8;21) inv(16)/t(16;16)	t(15;17) t(8;21) alone inv/del(16) and lacking unfav abn	t(15;17) t(8;21) inv(16)/t(16;16)
Intermediate	Normal Other non-complex	Normal +6, +8, -Y, del(12p)	Normal Other non-complex	Normal -Y	Normal Other non-complex	Normal Other non-complex	Normal Other non-complex
Adverse	abn(3q) -5/del(5q) -7 complex [≥ 5 unrel abn] Excluding those with favorable changes	abn(3q),(9q),(11q),(21q) abn(17p) -5/del(5q) -7/del(7q) t(6;9) t(9;22) complex [≥3 unrel abn]	inv(3)/t(3;3) -7 t(6;9) t(6;11) t(11;19) +8 complex (≥ 3 unrel abn) Excluding those with favorable changes	Other	inv(3)/t(3;3) -5/del(5q) -7/del(7q) abn(11q23) del(12p) abn(17p) complex (≥ 3 unrel abn)	abn(3q) -5/del(5q) -7/del(7q) abn(11q23) t(6;9) t(9;22) complex (≥ 3 unrel abn)	abn(3q) [excluding t(3;5)] inv(3)/t(3;3) add(5q)/del(5q)/ -5,-7/add(7q) t(6;11) t(10;11) t(9;22) -17 abn(17p) with other changes Complex (> 3 unrel abn) Excluding those with favorable changes

Unrel abn indicates unrelated abnormality; abn, abnormal.

Table 3. Classification of different cytogenetics risk groups in major cooperative groups clinical trials. (Grimwade & Hill , 2009).

3.1 Favorable risk

Acute promyelocytic leukemia (APL) with t(15;17) translocation as well as AML with core binding factor (CBF) abnormalities [t(8;21) and inv(16)/t(16;16)] fall in the favorable risk group. They represent around 15% of all AML cases in adults. The favorable outcome in this group has been consistently reported by different research group trials. See Figures 7 and 8.

3.1.1 t(15;17)

APL represents a distinct subtype of AML with characterstic morphological features, clinical presentation, and treatment regimen that incorporates all trans retinoic acid (ATRA). Different clinical trials have reported excellent outcomes with CR rates of more than 90 %. If an ATRA-based regimen of induction, consolidation, and maintenance is used, rates of 3-year OS exceed 85 %. In one report from European APL group 10-year OS rate was 77%. (Ades et al. 2010; Lo-Coco et al. 2010; Sanz et al. 2010) While it carries a good prognosis in general, it is important to

notice that patients with age less than 30 years and WBC count less than 10,000/microL at presentation have superior event-free survival. (Asou et al., 1998)
About 40% of patient with APL have associated chromosomal abnormalities. These additional abnormalities have no impact on treatment outcome. (De Botton et al., 2000; Slack et al., 1997)

3.1.2 t(8;21)

It has been consistently reported to be of favorable prognosis with with CR rates exceeding 87-90% and a 5-year survival of at least 40-65% (Grimwade et al., 2010; Appelbaum et al., 2006a). Along with AML with Inv(16)/ t(16;16), AML with t(8;21) comprise CBF leukemias. In addition to sharing similar pathogenesis, the CBF leukaemias share the characteristics of sensitivity to high-dose cytarabine (HDAC) (Grimwade et al., 1998; Slovak et al., 2000; Byrd et al., 2002). Furthermore, the outcome can be improved substantially by post-remission therapy with HDAC. (Byrd et al., 1999; Palmieri et al., 2002)
While there is agreement on prognosis in AML with isolated t(8;21), there has been inconsistently when defining the prognostic significance of additional cytogenetic abnormalities. Three different small trials have showed poor prognosis with the presence of deletions of the long arm of chromosome 9 (del(9q)) (Schoch et al., 1996) and karyotype complexity (Appelbaum et al., 2006b). On the other side, one large cohort showed no negative impact on prognosis; on the contrary, loss of the Y chromosome in male subjects was associated with a trend for better overall survival (Grimwade et al., 2010).
On the other hand, adverse prognostic significance has been linked to high WBC or absolute granulocyte count, the presence of granulocytic sarcomas, expression of the neural cell adhesion molecule CD56 on leukemic blasts and high WBC index. (Nguyen et al., 2002)

3.1.3 Inv(16)/ t(16;16)

While it is commonly grouped with AML associated with t(8;21) due to similar pathogenesis and outcome, there are few differences. AML associated with inv(16) has different morphological features usually of FAB M4Eo morphology and is less likely to have secondary cytogenetic changes (Byrd et al., 1999, 2004; Nguyen et al., 2002; Delaunay et al., 2003). The presence of such abnormalities, particularly +22, predicted a better outcome in AML associated with inv(16), t(16;16). (Schlenk et al., 2004; Marcucci et al., 2005)
As with t(8;21), the outcome of adults with AML with Inv(16)/ t(16;16) can be improved substantially by intensive post-remission therapy with HDAC. Byrd et al reported the 5-year relapse rate was significantly decreased in patients with inv(16)/t(16;16) receiving 3–4 cycles of HDAC as compared with those receiving one HDAC course (43% versus 70%) (Byrd et al., 2004)
Inferior outcome has been reported in patients presenting with high WBC counts (Martin et al., 2000) and older age. (Delaunay et al., 2003)

3.2 Intermediate risk

This comprises the largest cytogenetics group of AML patients. This is because it includes patients excluded from favorable and adverse groups. This translates in wide variation of CR and survival rates. It is believed to be molecularly heterogeneous and advances in molecular analyses of leukemic cell helped identifying subgroups in this large

heterogeneous group. This is particularly important in the largest subset of this group, patient with normal cytogentics AML.

3.2.1 Normal karyotype

The proportion of adults with de novo AML with normal cytogenetics (AML-NC) has varied between 40% and 49% in various clinical trials which makes the largest cytogenetically defined group of patients.

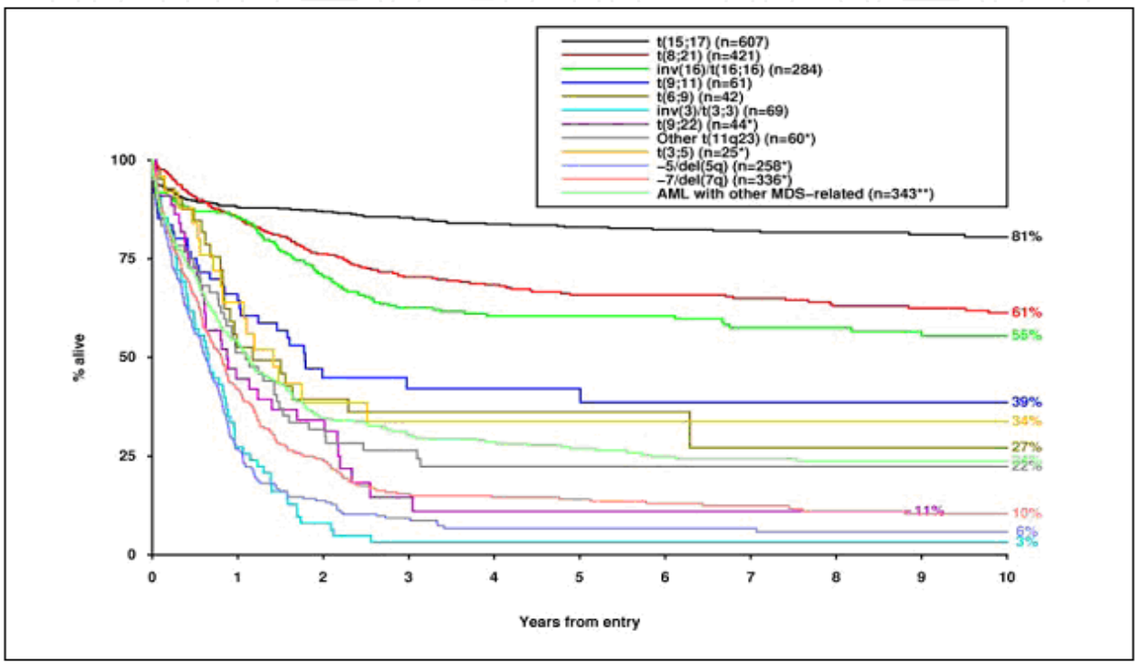


Fig. 8. Survival curves according to different cytogenetic aberrations for patients treated in MRC AML trials (AML10, 11, 12, 14 and 15) with t-AML and de novo AML (Grimwade & Hill , 2009).

While it is considered as one category in the intermediate risk group, AML-NC represents a heterogeneous group of patients as evident by the wide range of OS rates from 24% to 42%. (Gregory et al., 2009). While certain molecular abnormalities have been identified in AML-NC with prognostic significance that identify distinct subgroups of patients, further efforts are needed to subcategorize the rest of the patients in this heterogeneous group.

3.2.2 Trisomy 8

The prognosis of AML patients with trisomy 8 alone or with other aberrations is still a controversial issue. CR rates of patients with trisomy 8 have differed widely, from 29% to 91% (Schiffer et al., 1989; Dastugue et al., 1995). As a result, some groups such as the MRC and SWOG have assigned these patients to a intermediate risk group whereas the GALGB group consider trisomy 8 in the an unfavorable risk group, See table 3. The differences in prognosis of patients with trisomy 8 reported indicate that this population of patients is heterogeneous and identification of additional prognostic factors are needed.

3.2.3 Others

AML with other non-complex aberrations has been categorized in intermediate risk group due to CR and survival rates that fall between the other two major risk groups. MRC data showed a 10 year survival rate of 37% in patients with less than three aberrations not classified in other risk groups as compared to 38% in patients with normal karyotype, see figure 9b.(Grimwade et al.,2010)

3.3 Adverse risk

10-20% of AML patient have adverse risk cytogenetics. These patients tend to be older, often with a prior history of MDS or exposure to chemotherapy . Different trials have reported CR rates of less 60% and a 5-year survival of around 10%. (Grimwade et al., 2010; Byrd et al., 2002; Slovak et al., 2000)

While there is some variability in additional karyotypes defining unfavorable cytogenetics among different cooperative groups (See table 3), there is agreement on abnormalities of chromosomes 5 and 7 (monosomies of 5 and/or 7 (−5/−7) and deletions of 5q and 7q) ,chromosome 3 abnormalities (inv(3)/t(3;3) and 3q abnormalities except t(3;5)), and complex karyotype.

3.3.1 Chromosome 3 abnormalities

AML with inv(3)/t(3;3) represents approximately 1% to 2% of AML. CR rate has been reported to be < 50% with long term OS < 10%. (Grimwade et al., 2010; Byrd et al., 2002; Slovak et al., 2000). Advanced age and high WBC counts at diagnosis seem to confer an even worse outcome (Weisser et al., 2007).

As part of MDS-related cytogenetic abnormalities per 2008 WHO classification (Swerdlow et al., 2008), all 3q abnormalities have been associated with poor prognosis except for t(3;5). t(3;5) is a rare translocation associated with formation of the NPM1-MLF1 fusion gene. Clinically it occurs mainly occur in younger patients with a median age of 30 years and has a favorable outcome with CR rate exceeding 95%.(Grimwade et al., 2010)

3.3.2 Chromosome 5, 7 abnormalities

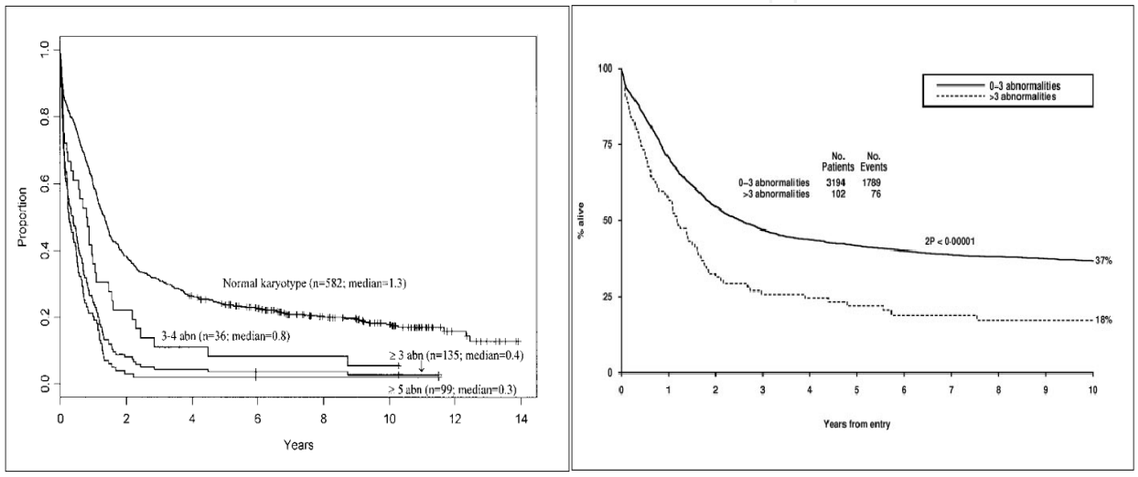
Aberrations of chromosomes 5 and 7 (-7/-5, 5q-, 7q-) are seen in 5% and 10% of cytogenetically abnormal AML respectively. There are usually associated with complex karyotype and rarely occur as a sole aberration. There are associated with MDS as well as t-AML related to alkylating agents and radiation. Prognosis is poor especially when part of complex karyotype, see Figure 8. On exception to that if these abnormalities are associated with favorable cytogenetic changes (t(15;17), t(8;21 and inv(16)/t(16;16)). (Heim & Mitelman, 2009)

3.3.3 Complex karyotype

The definition of complex karyotype differs between major cooperative groups while MRC defines it as the presence of a clone with at least five unrelated cytogenetic abnormalities , SWOG/ECOG, CALGB and AMLCG all go with three or more abnormalities. Although the outcome of patients with three or four abnormalities [other than t(8;21), inv(16)/t(16;16) or t(9;11)(p22;q23)] was better when compared to that of patients with five or more abnormal ties, both were grouped together due to the dismal prognosis in both (See figure 9).

3.3.4 11q23

Aberrations of chromosome band 11q23 occur in approximately 5% to 10% of adults with AML. In the current WHO classification, AML with these aberrations are regarded as a distinct entity. These aberrations occur in de novo as well as in therapy-related AML especially after treatment with topoisomerase II inhibitors. Aberrations of 11q23 commonly affect the MLL gene (also called HTRX, HRX, TRX1,and ALL-1). A special feature of the MLL translocations in AML is the large diversity of fusion partners. More than 50 different partner genes on various chromosomes have been described. The most common of those are *AF9* in the t(9;11) and *AF6* in the t(6;11). (Krauter et al. , 2009).



(a) (b)

Fig. 9. Survival curves according to the complexity of cytogenetics. a: Patients treated in CALGB 8461, tria l(Byrd et al., 2002) b: Patients treated in MRC AML trials (AML10, 12, and 15) (Grimwade et al., 2010).

While initially regarded of poor prognosis as a whole group, outcome of AML with 11q23 band aberrations differs according to the fusion partner. While t(6;11)(q27;q23) and t(10;11)(p12;q23) are associated with a poor prognosis in a number of studies (Martineau et al., 1998; Grimwade et al., 2010; Blum et al., 2004), t(9;11)(p22;q23) is considered of intermediate prognosis. Different trials have shown CR rates of of 79-84% and 10-year survival of about 39%. (Grimwade et al., 2010; Byrd et al., 2002)

4. Gene mutations

As previously stated, AML is a heterogeneous disease with variable outcome in each subgroup. Recent advances in molecular technology have revolutionized our understanding of AML biology and prognosis. It has been of great help in defining biological and clinically discrete subgroups especially in the heterogeneous group of AML-NC. It also provides new insight on new possible therapeutic targets. The impact of newly recognized gene mutations on the understanding of AML biology is evident by adding provisionally new subtypes of AML in the new WHO classification of myeloid neoplasms (i.e. AML with mutated NPM1

and AML with mutated CEBPA) (Swerdlow et al., 2008). The prognostic significance of certain mutation is evident by the new genetic risk grouping proposed by European LeukemiaNet (ELN) which divide AML-NC to subgroups according to associated mutations and put them in different risk groups. (Dohner et al., 2010)

4.1 FLT3

FMS-like tyrosine kinase 3 (*FLT3)* gene encodes a member of the class III receptor tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells and plays an important role in the survival and differentiation of multipotent stem. First described by Nakao et al in 1996, mutations in FLT3 are among the most common genetic mutations in AML with prevalence of 30 - 40% (Nakao et al, 1996; Gregory et al., 2009).
Mutations affect one of two functional domains of the receptor, the juxtamembrane domain (JMD) and the activation loop of the tyrosine kinase domain (TKD). The most common mutation in the JMD of the FLT3 gene is internal tandem duplications (FLT3-ITD) involving JMD with a prevalence of about 25% of adult AML patients. It is particularly more common in AML-NC and AML with t(15;17) where it is reported to in 28-38% and 20-35% respectively. Point mutations affecting TKD and JMD have been reported in about 5-10% and 2% of all AML patients respectively. (Marcucci et al., 2011; Thiede et al., 2002; Schnittger et al., 2002, Mrozek et al., 2007) Clinically, *FLT3*-ITD–positive patients present with increased WBC counts and are more often diagnosed
with de novo than secondary AML. While CR rates are comparable to unmutated AML-CN, prognosis is poor due to high relapse risk. The adverse outcome seen is related to the size of ITD. The longer the duplication the worse the prognosis. (Gregory et al., 2009)
In contrast to FLT3-ITD mutations, the prognostic significance of FLT3-TKD mutation is still controversial with conflicting conclusions from various studies (Mead et al., 2007; Whitman et al., 2008). In another report from Bacher et al., a neutral impact was seen when looking at all patients with TKD mutation. However in the presence of NPM1 or CEBPA mutation a favorable impact was observed and a negative impact was seen if a TKD mutation occurred in conjunction with MLL-PTD, t (15;17) or FLT3-ITD. (Schlenk et al. 2008, Bacher et al., 2008)
In addition to being a prognostic marker, FLT3-ITD is a potential therapeutic target. Several small-molecule inhibitors of FLT3 tyrosine kinase activity in combination with chemotherapy as a frontline therapy for patients with FLT3 mutation are currently evaluated in phase III clinical trials (Marcucci et al., 2011)

4.2 NPM1

Nucleophosmin (NPM1) is nucleocytoplasmic shuttling protein mainly localized in the nucleolus that has multiple functions involved in cell proliferation, apoptosis, DNA repair and ribosome biogenesis. The NPM1 gene belongs to a new category that functions both as an oncogene and tumor-suppressor gene, depending on gene dosage, expression levels, interacting partners, and compartmentalization. First reported by Falini et al in 2005, NPM1 mutations are very common as they are present in 50% to 60% of patients with AML-NC. (Falini et al, 2005; Gregory et al., 2009; Foran 2010)
Clinically, NPM1 mutations are associated with specific features, including predominance of female sex, higher bone marrow blast percentages, LDH levels, WBC and platelet counts, and high CD33 but low or absent CD34 antigen expression. NPM1 mutations tend to be stable over the disease course, supporting their role as primary lesions in leukemogenesis

and accordingly is recognized as a provisional entity in the 2008 revision of the WHO classification of myeloid neoplasms and acute leukemia. (Swerdlow et al., 2008).
Of notice, FLT3-ITD mutation is detected in approximately 40% of patients with NPM1 mutations. Mutated NPM1 without concurrent FLT3-ITD has been associated consistently with achievement of CR and favorable outcome comparable to CBF AML. (Smith et al., 2011). On the basis of this observation, AML with mutated NPM1 without FLT3-ITD has then recently been allocated to the genetic favorable-risk category of AML together with CBF AML in the new classification suggested by ELN. On the other hand, NPM1 mutations did not impact the poor outcome of patients with FLT3-ITD mutation. (Marcucci et al., 2011; Foran 2010)

4.3 CEBPA

The transcription factor CCAAT enhancer-binding protein alpha (CEBPA) is a key molecule in the mediation of lineage specification and differentiation of multipotent myeloid progenitors into mature neutrophils. Mutations in CEBPA were first identified in AML in a report from Pabst et al in 2001 . Reports following indicate 5% to 10% of de novo AML have this mutation with higher prevalence in AML-NC (15-20%). (Pabst et al., 2001; Fröhling et al., 2004; Foran 2010)
AML-NC patients carrying a CEBPA mutation are characterized by distinct clinical features such as higher peripheral blood blast counts, lower platelet counts, less lymphadenopathy, or extramedullary leukemia. As compared to NPM1 mutations, CEBPA mutations are less frequently associated with FLT3-ITD or TKD mutations. (Schlenk et al., 2008)
In the absence of a FLT3-ITD, CEBPA mutation has a favorable prognosis in patients with AML-NC with approximately 60% long-term survival. Prognosis is better if the mutation is biallelic, where it is categorized in the favorable risk group. (Dufour et al., 2010; Foran 2010; Smith et al., 2011)

4.4 KIT

KIT is the receptor for stem cell factor (KIT ligand) and is expressed on less than 5% of marrow cells. KIT mutation is frequently noted in CBF leukemia with prevalence of 30-40% and 20-30% in inv(16)/t(16;16) and t(8;21) leukemia respectively.
Clinically, Patients affected appear to have higher WBC counts and higher frequency of extramedullary disease such as paraspinal masses. (Foran 2010; Smith et al., 2011). Recent trials have reported significantly higher incidence of relapse and significantly lower survival in CBF leukemia harboring KIT mutation (Schnittger et al., 2006; Baschka et al., 2006). Clinical trials are currently underway evaluating KIT inhibitors in CBF leukemias. (Marcucci et al., 2011)

5. Future perspectives

Advances in molecular studies have changed our understanding of AML as a single disease. As discussed in previous section , certain gene mutations has fragmented previously known risk groups into smaller and more homogenous groups. Identification of new mutations and understanding their prognostic and predictive value is a major goal in AML research. In addition, gene and microRNA expression profiling is a very active area of research in AML with interesting recent observations. We hope that such advances will provide us with more

information that will help in systematic characterization of cancer genomes. We will review briefly few areas of active research showing promising results that need further efforts before it has its practical implications as prognostic and predictive tools.

5.1 Gene mutations

Further gene mutations have been identified in recent trials which are still waiting further clinical data to support their prognostic implications.

5.1.1 IDH1/IDH2 mutations

IDH1/IDH2 gene mutations, which were first reported in gliomas with good prognostic impact, have been recognized recently in AML with aggregate frequency of these two mutations of about 15% to 20% of all patients with AML and 25% to 30% of patients with AML-NC. There are conflicting data concerning the prognostic significance of IDH mutations in AML, with some studies suggesting that they are associated with a poorer outcome especially in NPM1 mutated AML, while others have found no evidence of that (Marcucci et al., 2010; Thol et al., 2010). Further studies with larger number of patients harboring this mutation are needed to further characterize the prognostic significance of this rare mutation.

5.1.2 CBL mutation

The Casitas B-cell lymphoma (CBL) gene on chromosome 11q23.3 contains several functional domains. One of these domains, the C-terminal domain, gives rise to the CBL protein which has ubiquitin ligase activity that targets a variety of tyrosine kinases for degradation by ubiquitination. Heterozygous CBL mutations have been recognized in 0.6% to 33% of AML patient (Sargin et al., 2007; Bacher et al., 2010; Ghassemifar et al., 2011). Interestingly, CBF AML patients represented a significant proportion of patients who have this mutation. (Abbas et al., 2008; Reindel et al., 2009). In one retrospective review including more than two hundred AML patients along with similar number of MDS and MDS/MPD diseases, the presence of CBL mutation was an independent adverse prognostic factor for OS. (Makishima et al., 2009)

5.2 Gene expression profiling

In addition to structural genetic aberrations, changes in expression of specific genes seem to impact prognosis of molecular subsets of patients with AML. Increased or decreased expression of specific genes (typically those involved in hematopoiesis, myeloid differentiation, or immune response) has been associated with response to therapy as well as survival.

5.2.1 BAALC

The brain and acute leukemia cytoplasmic (BAALC) gene is localized on chromosome band 8q22.3. It has been postulated to function in the cytoskeleton network due to its cellular location. It is most commonly seen in AML with trisomy 8 and AML-NC. Several studies have demonstrated that high BAALC expression is a poor prognostic indicator in AML-NC for such factors as OS, DFS, and resistant disease. BAALC expression appears to be particularly useful as a prognostic marker in AML-NC patients lacking FLT3-ITD and CEBPA mutations. (Mrozek et al., 2007; Gregory et al., 2009)

5.2.2 MN1

The meningioma 1 (MN1) gene encodes a protein that participates in a gene transcription regulator complex involving retinoid receptors. Recent studies have shown MN1 overexpression is associated with poor prognosis in AML in terms of response to induction chemotherapy, relapse rate and therefore OS. Interestingly, one study has shown low MN1 expression was correlated with better response therapy in AML. Together, both observations suggest that MN1 expression is not only a prognostic but also a predictive marker for response to treatment. (Foran 2010; Marcucci et al., 2011)

5.2.3 ERG

The ETS-related gene (ERG) is a member of the ETS family of transcription factors. High ERG expression is associated with the upregulation of many genes which are involved in cell proliferation, differentiation, and apoptosis. ERG overexpression mostly impacted outcome of low molecular risk AML-NC (mutated NPM1 without FLT3-ITD) and AML with low BAALC expression. (Gregory et al., 2009; Marcucci et al., 2011)

5.3 MicroRNA expression

MicroRNAs are noncoding RNAs of 19 to 25 nucleotides in length that regulate gene expression. They perform critical functions in cell development, differentiation, proliferation, and apoptosis. They have been shown to play a role in malignant transformation in solid malignancies. Recent studies in AML have shown that specific patterns of microRNA expression are closely associated with certain cytogenetics and molecular changes like FLT3-ITD. Results are reproduced and such patterns are considered like signatures. For example in two separate studies, upregulation of microRNAs expression from genes localized at chromosome band 14q32 has been found in APL with t(15;17) while the downregulation of certain mircoRNAs (*miR-133a)* was observed in patients with t(8;21). In AML-NC, specific microRNAs expression signature (*miR-155)* was associated with the presence of high risk features (lack of NPM1 mutation or the presence of FLT3-ITD), while upregulation of microRNAs (*miR-181)* was identified in CEBPA mutated AML. (Foran 2010; Marcucci et al., 2011)

6. Conclusion

AML is markedly heterogeneous disease with variable response to therapy and survival. While advances in AML therapy have been moving slowly over last few decades, there have been dramatic breakthroughs in the identification of reproducible prognostic variables in AML. In particular, advances in molecular biology as well as genomics technology have revolutionized our approach to AML and have added substantially to our understanding of biology and prognosis of this disease through identification of novel prognostic markers. This is particularly important in AML-NC which comprises a large heterogeneous group of patients. While such advances help separating AML patients into smaller homogenous groups, we hope to look for a day where individualized therapy for patients AML can be tailored to achieve the best outcome. Such breakthroughs facilitate risk-stratified approach to therapy in AML where more groups are separated into favorable or poor risk groups rather staying the large grey intermediate group. They also provide us with insight into potential therapeutic targets that can be assessed in clinical trials on which we largely depend to achieve breakthroughs.

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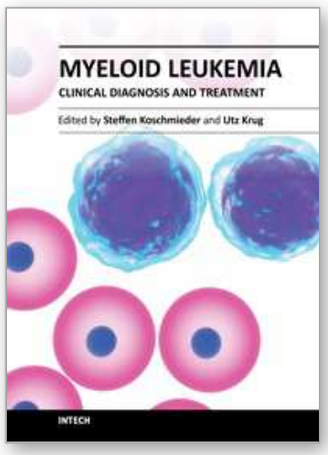

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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and chronic myeloid leukemias (CML) and original publications covering specific clinical aspects of these important diseases. Covering the specifics of myeloid leukemia epidemiology, diagnosis, risk stratification and management by authors from different parts of the world, this book will be of interest to experienced hematologists as well as physicians in training and students from all around the globe.

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