Cancer Research Journal
2018; 6(3): 74-78
http://www.sciencepublishinggroup.com/j/crj
doi: 10.11648/j.crj.20180603.11
ISSN: 2330-8192 (Print); ISSN: 2330-8214 (Online)

Management of Acute Myeloid Leukemia Patients Old than 60 Years in Casablanca: A Great Challenge in Developing Countries

Romaric Mahutondji Massi[1, *], Mouna Lamchahab[1], Bienvenu Houssou[1], Nheza Hda[1], Nisrine Khoubila[1], Siham Cherkaoui[1], Bouchra Oukkache[2], Asmaa Quessar[1]

[1]Department of Haematology and Paediatric Oncology, Faculty of Medecine and Pharmacy, Hassan II University, Casablanca, Morocco

[2]Department of Haematology Laboratory, Faculty of Medecine and Pharmacy, Hassan II University, Casablanca, Morocco

Email address:

massiroswork@yahoo.fr (R. M. Massi)

[*]Corresponding author

To cite this article:

Romaric Mahutondji Massi, Mouna Lamchahab, Bienvenu Houssou, Nheza Hda, Nisrine Khoubila, Siham Cherkaoui, Bouchra Oukkache, Asmaa Quessar. Management of Acute Myeloid Leukemia Patients Old than 60 Years in Casablanca: A Great Challenge in Developing Countries. *Cancer Research Journal*. Vol. 6, No. 3, 2018, pp. 74-78. doi: 10.11648/j.crj.20180603.11

Received: March 15, 2018; **Accepted**: April 2, 2018; **Published**: May 28, 2018

Abstract: Introduction**:** AML is the most common form of acute leukemia in adults, accounting for 25% of leukemias in this population in the Western world. The characteristics of AML in the elder patients are different from those in young patients characterized by a high prevalence of poor prognosis cytogenetic abnormalities. All these factors make AML in patients older than 60 years to be an particular entity wich management is very difficult in developing countries. Data on this group of AML patients are rare in our context and the Morocco national AML-MA 2011 protocol wich is use for the treatement of AML is limited for patients aged less than 60 years. The aim of our study was to describe the epidemiological, clinical, biological characteristics of AML patients aged over 60 in the departement and to highlight the dificulties wich occurred in their management. Patients and method: A retrospective study was conducted from 1 January 2003 to 1 January 2016 including, all cases of AML patients olders than 60 years, diagnosed according to WHO criteria. Conventional cytogenetics was made in RGH band on medullary or blood samples. Results: 266/1741 (15.28%) cases were recorded during the study. The median age was 70 years (61-98ans) and the sex ratio was 1.12. The median leukocyte count at diagnosis was 33,891 / mm3 (450-347000). 52/266 (20%) patients had hyperleucocytosis more than 50G/L at diagnosis. The mean hemoglobin level at diagnosis was 6.4 g / dl (3-10.3d / dl), the mean platelet count was 76525mm3 (5000-262000) 52/266 (20%) had hyperleucocytosis. 140 patients (52.6%) had a karyotype of which 3% favorable prognosis, 67% intermediate prognosis, and 30% unfavorable prognosis. Conclusion**:** AML patients old than 60 years represent an important part of AML patients in the departement. Their characteristics are the same like in literature with a dominance of intermediate prognosis group. Very few are treated with intensive chemotherapy in our series.

Keywords: Acute Myeloid Leukemia, Older, Characteristics, Management, Difficulties

1. Introduction

Acute myeloid leukemia (AML) is a group of clonal hematopoietic stem cell disorders characterized by overproliferation of undifferentiated myeloid cells, known as myeloblasts. AML is the most common form of acute leukemia in adults, accounting for 25% of leukemias in this population in the Western world [1].

The incidence of AML is expected to increase as a result of the aging of the population, a rise in secondary cases from environmental exposures, and wider recognition that low blood counts may be indicative of a bone marrow disorder rather than a normal consequence of aging. SoAML is considered to be a disease afflicting an older adult population.

According to USA National Cancer Institute, in 2008, the median age at the diagnosis was 67 years [2]. Compared with patients younger than 60 years, older adult patients with

AML have poorer survival outcomes. Although patients younger than 45 years have five-year overall survival of 38%, the rate declines to 8% in patients aged 60–69 years and abruptly falls to 0% for those 80 years or older [3].

AML in older adult patients is generally more drug resistant, more likely to be preceded by myelodysplasia, and more often associated with unfavorable cytogenetic abnormalities [4]. In general, older adult patients may be less tolerant of the toxicities associated with standard cytarabine-based induction and consolidation chemotherapy, possibly because they typically present with comorbid conditions. By one estimate, more than 25% of patients with cancer aged 75 years or older have at least six comorbidities [5].

To add Appelbaum et al, found in 2006 that the frequency of early deaths (occurring within the first 30 days of remission induction) increased dramatically in patients with a baseline performans status of 2 or higher as their age advanced. For example, among patients with a PS of 2, early mortality rates increased from 2% in patients younger than 56 years to 18%, 31%, and 50% in those aged 56–65 years, 66–75 years, and older than 75 years, respectively [4].

All these factors make AML in patients older than 60 years to be an particular entity wich management is very difficult in developing countries. Then it is necessary to study carefully the characteristics of these patients in order to propose them the adequate treatment. Data on this group of AML patients are rare and the Morocco national AML-MA 2011 protocol wich is use for the treatement of AML is limited for patients aged less than 60 years.

The aim of this study was to describe the epidemiological, clinical, biological characteristics and outcome of AML patients aged over 60 in the departement and to highlight the dificulties wich occurred in their management.

2. Patients and Methods

A retrospective study was conducted from 1 January 2003 to 1 January 2016 including, all cases of AML patients olders than 60 years, diagnosed according to WHO criteria. Immunophenotyping was done in differents centers. Conventional cytogenetics was made in RGH band on medullary or blood samples. Hyperleucocytosis forms were defined as having a white cell count ≥ 50G / L.

For intensive chemotherapy, two treatment periods were considered. From 2003 to 2010, patients were treated according to the AML-MA 2003 protocol (two induction cycles based daunorubicin (50 mg / m^2 03 days) and Ara-C (200mg / m2 by continuous infusion for 7 days) followed by the consolidation based on Ara-C (2g / m^2 / 12 h for 4 days) and Asparginase 6000UI / m^2).

From 2011 to 2014 patients were treated according to the AML-MA 2011 protocol (two induction cycles based daunorubicin (50 mg / m^2 03 days) and Ara-C (100mg / m^2 / 12h for 10 days) with more of etoposide (100 mg / m^2 for 5 days) for the second induction followed by three consolidations based on high doses of Ara-C (3g / m^2 / 12h for 3 days) combined with Daunorubicin (30mg / m^2 02 days) for the first and third**;** the Asparginase 6000UI / m^2 for the second**.** All patients had received neurological prophylaxis.

The supportive care (transfusions, anti infectious adapted to the ecology of the departement) were administered case by base.

For metronomic treatment, patients had received low dose of cytarabin associated with 6-MP or hydroxyurea per os and supportive care like in intensive chemotherapy. The analysis of data was performed by SPSS 18.7

3. Results

266/1741 (15.28%) cases were recorded during the study. The median age was 70 years (61-98ans) and the sex ratio was 1.12. (Figure 1). 147 (55.2%) patients had differents comorbidities: 15 (5.6%) were diabetics, 34(12.8%) had high blood preasure, 17 (6.4%) had heart insufficiency, 23 (8.6%) had Kidneyinsufficiency (Table 1). The initial clinical presentation is summarized in table 2. 89 (33%) patients had complete bone marrow insufficiency and 165 (62%) had incomplete bone marrow insufficiency. 163 (61.2%) had Performans Status ≥ 2. (Figure 2). The median leukocyte count at diagnosis was 33,891 / mm3 (450-347000). 52/266 (20%) patients had hyperleucocytosis more than 50G/L at diagnosis. The mean hemoglobin level at diagnosis was 6.4 g / dl (3-10.3d / dl), the mean platelet count was 76525mm3 (5000-262000), 52/266 (20%) had hyperleucocytosis. According to bone marrow cytologically study, it noticed: 85 cases (32%) of M2, 67 cases (25%) of M1, 57 cases (21%) of AML / MDS, 19 cases (7%) M4, 17 cases (6%) of Mo, 9 cases (4%) of M5, 8 cases (4%) M6 and 4 (2%) cases of M7 (Figure 3). 140 patients (52.6%) had a karyotype of which 3% favorable prognosis, 67% intermediate prognosis, and 30% unfavorable prognosis (Table 3). 20 patients (8%) were treated with intensive chemotherapy and 246 (92%) had received a metronomic treatment. For patients treated with intensive chemotherapy, 9 (45%) were in CR after induction I, 6 (30%) were not in complete remission, and 5 (25%) had died during treatment.

Table 1. *Distribution of patients according to comorbidity.*

Commorbidity	n	%
Breast cancer	7	2.6
Prostate cancer	9	3.3
Diabetics	15	5.6
High blood preasure	34	12.8
Hip fracture	4	1.5
Heart insufficiency	17	6.4
Kidneyinsufficiency	23	8.6
Tobacco	27	10.1
Tuberculosis	11	4.10
No commorbidity	119	44.7

Table 2. *Distribution of patients according to initial clinical presentation.*

Clinical presentation	n	%
Bone pain	7	3
Isolated tumor syndroma	5	2
Complete bone marrow insufficiency	89	33
Incomplete bone marrow insufficiency	165	62

Table 3. *Distribution of patients according to karyotype.*

Cytogenetics abnormalities	n	%
Favorable prognosis		
t(8;21)	2	1.4
t (15;17)	1	0.7
Inversion 16	1	0.7
Unfavorable prognosis		
Del 11q23	4	2.8
Monosomy 7	4	2.8
Monosomy 5	2	1.4
Karyotype complexe	32	23
Intermediate prognosis		
Trisomy 8	6	4
Trisomy 7	4	2.8
Loss of sexual chromosom	2	1.4
Del 8	3	2
Trisomy 21	3	2
Normal Karyotype	62	45
Other	14	10

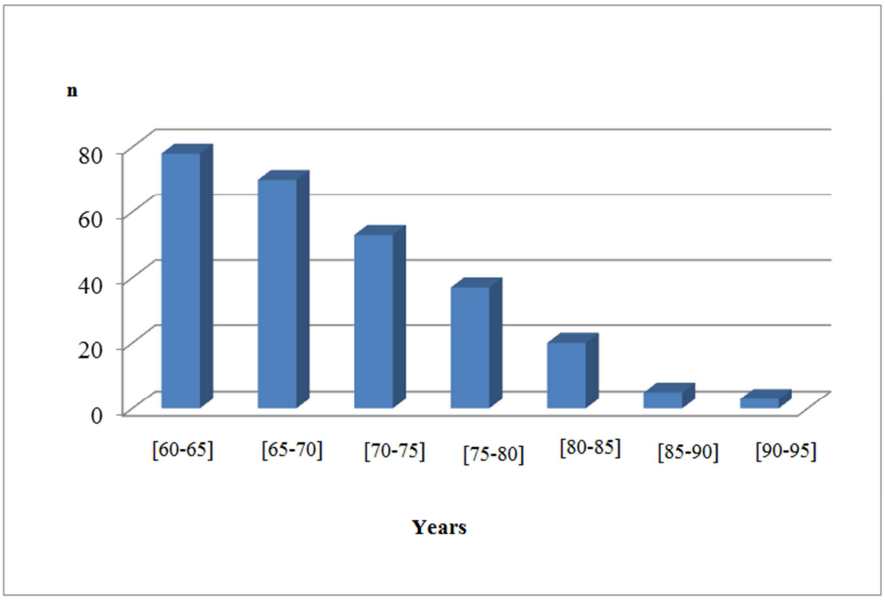

Figure 1. *Distribution of patients according to age.*

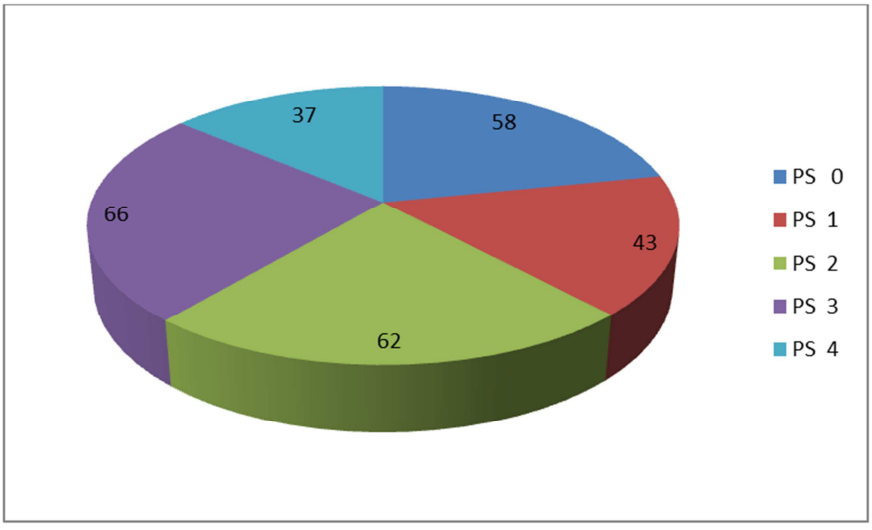

Figure 2. *Distribution of patients according to Performans status.*

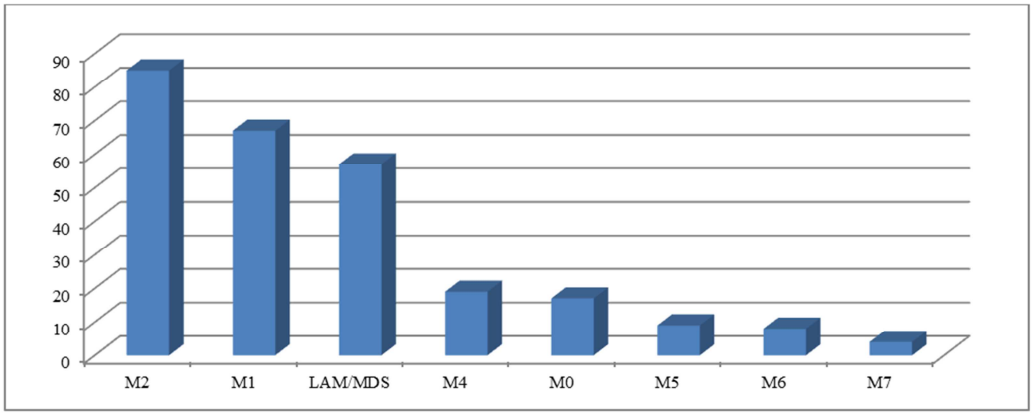

Figure 3. *Distribution of patients according to Cytologically study.*

4. Discussions

The treatment of older patients with AML is among the most challenging dilemmas for hematologists. In fact, acute myeloid leukemia in older patients presents special problems because of patient characteristics as well as the unique biologic behavior of the leukemic cells in this patient population. Older patients tend to have comorbid conditions that compromise cardiac, pulmonary, renal, hepatic, and other organ functions, reducing their ability to tolerate optimal doses of chemotherapy.

The leukemic cells in older patients with AML tend to be more resistant to conventional chemotherapeutic agents because of a variety of factors**:** higher incidence of poor prognostic chromosomal abnormalities, increased expression of multidrug resistance compared with younger patients [6]. Many of these patients have pre-existing myelodysplastic syndrome, which also reduces the ability to achieve and maintain remission after antileukemic therapy. An other reason wich explain the difficulty to treat olders AML patients is that they have poor performance status (PS). Review of data from 437 patients who entered into treatment in Southwest Oncology Group (SWOG) studies shows that by the time the patients are aged > 75 years, the proportion of patients with poor PS has doubled [4]. It is therefore necessary to study currently the characteristics of this group of patients in order to proposed for them an appropriate and therapeutic.

That is the aim of this study wich had included 266 patients aged than 60 years old and up light that older AML patients represent 15% of AML patients treat in the departement. The median age approch data in literature (70 years) but is higher than the median age show by a recent russian series (286 patients) in 2015 wich found 64.9 years [7]. The distribution of patients age shows that more than half (51%) of the patients had between 60 and 70 years. This subgroup could benefit from intensive chemotherapy if a good stratification is realised. The sex ratio wich was 1.12 showed a little predominance of male patients.

More than half of patients had one commorbidity (diabetic, high blood preasure, Kidney insufficiency, heart insufficiency) which can compromise tolerance to conventional chemotherapy. Then it is necessary to realized a good risk stratification for this older adults with AML according to international recommendations in order to discriminate between those older adults who are fit for intensive therapies and those who are vulnerable and may experience excess toxicity.

Fifty per cent of the patients had a performance status less than or equal to 2. This observation confirm the necessity to do a good risk stratification for this patients because poor performance status is an important prognostic factor in older adult patients. It increase the frequency of early deaths in aged AML patients [4].

The median white blood cells count at diagnosis (33 G/L), the median platelet count (76 G/L) were higher than the median showed by Jakson K. and al series (345 patients) wich was respectively 4.5G/L and 68G/L. But the median of hemoglobin level in the same study (9.1g/dl) is higher than the rate showed in our series wich was 6.4 g/dl [8].

Only the half of patient (52%) had a karyotype because before 2015 it was not done systematically for older patient. Actually all patient with AML have karyotype systematically. The prognosis according to cytogenetics abnormalies is dominate by intermediate group (67%), and unfavorable group (30%). Jakson K. and al found the same think with respectively 64% and 31%. Only 3% of patients had good prognosis in Karyotype versus 14% in young patients with AML in our unit. This confirm that adverse prognosis predominate in olders patients. It is therefore necessary to proceed molecular biology to identify good prognosis patients in intermediate prognosis group. In 2015, Zhao XL and al studies show thatthe incidences of FLT3, NPM1, C-Kit, CEBPα, DNMT3A mutation were 12.57%, 22.06%, 2.16%, 14.71%, 15.71% respectively in elder AML patients [9]. Some recent systematic review and meta-analysis evaluate the prognostic value of mutations in the NPM1, CEBPA, and FLT3 genes. FLT3-ITD was associated with worse prognosis, whereas mutations in NPM1 and CEBPA genes were associated with a favorable prognosis [10-12]. So some elder patients with NPM1 and CEBPA mutations can be treated by intensive chemotherapy.

Yanada M and al study show in 2012 that 50% olders patients with AML wich are able and received intensive

chemotherapy achieve complete remission [13]. Then older patients who are 'fit' for intensive chemotherapy and would have a reasonable chance to benefit based on host and disease characteristics should receive standard induction chemotherapy with 7 days of continuous infusion of cytarabine and at least 60 mg/m(2) daunorubicin daily for 3 days.

On the other hand, hypomethylating agents, such as azacytidine and decitabine offer the possibility of long-term disease control without necessarily achieving complete remission and can represent a reasonable alternative to intensive chemotherapy [14-15].

In this series, only a few group of patients (8%) received intensive chemotherapy because they are not a treatement protocol for older patient and the AML-MA-2011 protocol currently use is limited for patients aged less than 60 years. Only few patient with good prognosis in karyotype receive intensive chemotherapy. So it is necessary to introduce commorbidity scoring and molecular biology in order to identify the patients with good prognosis and to treat them with intensive care.

5. Conclusion

AML patients old than 60 years represent an important part of AML patients in the departement. Their characteristics are the same like in literature with a dominance of intermediate prognosis group. Very few are treated with intensive chemotherapy in our series.

This study up light that more than fifty per cent of the patients had between 60 and 70 years and PS ≤ 2. We think that patient in this subgroup must receive intensive therapy when having a good commorbidity scoring. Thus it is necessary to introduce in the management of older AML patients in the departement, the commorbidity scoring and molecular biology in order to identify the patients with good prognosis and propose them for intensive care. The management of patients wich are ineligible for intensive care must also be improved by using agents, such as azacytidine and decitabine.

Declarations

The article has been read and approved by all authors.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

References

[1] B. Deschler, G. Ihorst, M. Kuhn, B. Ruter, M. Lubbert. Geriatric assessment: a prospective study in older patients with AML and high-risk MDS. Critical Reviews in Oncology/Hematology 60 (2006): 26-7

[2] Barbara B. Roger. Advances in the management of Acute Myeloid Leukemia in Older Adults Patients. Oncology Nursing ForumVol. 37, No. 3, May 2010: 168-179.

[3] S. S. Farag, K. J. Archer, K. Mrozek, A. S. Ruppert, A. J. Carroll, J. W. Cardiman and al. “Pretreatment Cytogenics Add to Other Prognostic Factors Predicting Complete Remission and Long-Term Outcome in Patients 60 Years of Age or Older With Acute Myeloid Leukemia: Results From Cancer and Leukemia Group B 8461. 2006, Blood, 108, p. 68.

[4] Frederick R. Appelbaum, Holly Gundacker, David R. Head, Marilyn L. Slovak, Cheryl L. Willman, John E. Godwin, and al. Age and acute myeloid leukemia. Blood, 1 may 2006 volume 107, number 9: 3481-5.

[5] Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. Cancer 1997 Oct 1; 80(7):1273-83.

[6] Mauritson N, Johansson B, Albin M, et al. Survival time in a population-based consecutive series of adult acute myeloid leukemia: the prognostic impact of karyotype during the time period 1976-1993. Leukemia 2000; 14:1039-43.

[7] Semochkin SV, Tolstykh TN, Arkhipova NV, Ivanova VL, Kliueva OV, Lunin VV and al. Clinical and epidemiological characteristics of acute myeloid leukemias in adults according to the data of municipal hematology departments in Moscow. Ter Arkh. 2015; 87(7):26-32.

[8] Kathryn JACKSON, Glen KENNEDY, Peter MOLLEE, Paula MARLTON and Kirk MORRIS. Intensive chemotherapy and reduced-intensity allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia in elderly patients. Asia-Pacific Journal of Clinical Oncology 2014; 10: 246–254.

[9] Zhao XL, Liu KQ, Lin D, Wei H, Wang Y, Zhou CLand al. Characteristics of karyotypes and gene mutations for elder acute myeloid leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2015 Apr; 23(2):300-5.

[10] Marcucci G, Maharry K, Radmacher MD, Mrózek K, Vukosavljevic T and al. Prognostic significance of, and gene and microRNA expression signatures associated with, CEBPA mutations in cytogenetically normal acute myeloid leukemia with high-risk molecular features: a Cancer and Leukemia Group B Study. J Clin Oncol. 2008 Nov 1; 26(31):5078-87.

[11] Becker HGanser A, Marcucci G, Maharry K, Radmacher MD, Mrózek K, Margeson D and al. Favorable prognostic impact of NPM1 mutations in older patients with cytogenetically normal de novo acute myeloid leukemia and associated gene- and microRNA-expression signatures: a Cancer and Leukemia Group B study. J Clin Oncol. 2010 Feb 1; 28(4):596-604.

[12] Port M, Böttcher M, Thol F, Schlenk R, Wasem J, and al. Prognostic significance of FLT3 internal tandem duplication, nucleophosmin 1, and CEBPA gene mutations for acute myeloid leukemia patients with normal karyotype and younger than 60 years: a systematic review and meta-analysis. Ann Hematol. 2014 Aug; 93(8):1279-86.

[13] Yanada M, Naoe T. Acute myeloid leukemia in older adults. Int J Hematol. 2012 Aug; 96(2):186-93.

[14] Ferrara F. Conventional chemotherapy or hypomethylating agents for older patients with acute myeloid leukaemia? Hematol Oncol. 2014 Mar; 32(1):1-9.

[15] Tawfik B, Sliesoraitis S, Lyerly S, Klepin HD, Lawrence J, Isom S. Efficacy of the hypomethylating agents as frontline, salvage, or consolidation therapy in adults with acute myeloid leukemia (AML). Ann Hematol. 2014 Jan; 93(1):47-55.