Original Article

Experience with treatment of fifty eight Iraqi patients with Acute Myeloid Leukemia

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Summary:

Background: Adults with Acute Myelogenous Leukemia (AML) have the lowest survival rate of all leukemias. Complete remission (CR) rate after induction therapy is about 55-85%, however 30% of patients fail to achieve remission and they remain alive only for about a year. Consolidation chemotherapy results in 5-year overall survival (OS) of about 30%.

Objectives: To study characteristics of adult patients with AML who attended Baghdad Teaching Hospital, their response to induction therapy and then to consolidation therapy, and their 5-year (OS) and disease free survival (DFS).

Patients and methods: Sixty seven patients with AML (excluding M3) were admitted to the haematology ward /seventh floor/Medical city teaching hospital during 2008 with follow up till the end of 2012. Fifty eight patients included in the study, 47 patients (≤ 60-year) received 3+7 induction regimen. Nine (> 60 year) received attenuated courses of subcutaneous cytosar, or 2+5 regimen (according to presence or absence of co-morbidities). Those who attained CR were consolidated mainly with Modified MiDAC.

Results: Eleven patients who received attenuated induction therapy had a median survival of 6-8 months and none of them achieved CR. Twenty six (55.5%) out of 47 patients who received 3+7 induction regimen had CR with treatment related mortality(TRM) of 34%, while OS and DFS were 30% and 34% respectively.

Conclusion and recommendation: Early referral to the hospital is essential to avoid high early mortality. OS and DFS in our study is comparable to other studies in spite of shortage of antibiotics and cytotoxic therapy.

Key words: AML, induction, consolidation, OS, DFS.

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Introduction:

Acute myeloid leukemia (AML) is a heterogonous disease with a variable outcome. Unsatisfactory outcomes persist for the majority of patients particularly the elderly. It is the most common acute leukemia and accounts for approximately 80%(1). In the United States and Europe the incidence has been 3-5/100000 population(2). Untreated, is uniformly fatal disease with a median survival time shorter than three months. Current treatment increases survival time for most patients, some of whom may be cured(3). Despite significant progress, the outcome is variable and often suboptimal, younger patients tend to be far better and some series suggest that about 50% of patients < 40 year of age are cured, where as those > 60 year old, only 10-15% will be alive 1 year after diagnosis(4).Secondary leukemia is a poorly defined term that often refers to the development of AML following the history of previous diseases such as myelodysplastic syndrome (MDS), or chronic myeloproliferative disorders, or secondary to treatment with chemotherapy or radiotherapy. Survival of therapy related (t-AML) is generally shorter than those with de novo AML within the same genetic group(5).Patients usually present with symptoms related to complications of pancytopenia (e.g.anaemia, neutropenia, and thrombocytopenia)(6).

Induction chemotherapy with 3+7 remains the standard treatment for patients less than sixty years with newly diagnosed AML(7). This treatment results in severe pancytopenia in all patients and therefore requires transfusion support and antibiotics as needed. The median number of days with absolute neutrophil count < 0.5X109/L and a platelet count < 50X109/L are approximately 16 and 15 respectively(8).Substantial burdens of leukemic cells remain undetected (i.e. the presence of minimal residual disease) after induction leading to relapse within few weeks or months if no further chemotherapy is administered(9), so additional cytotoxic therapy is mandatory after successful remission to eradicate the residual disease. Increasing the intensity of this consolidation treatment is beneficial in younger but not in older adults(10). In AML 15 trials, the consolidation regimen which included Mitoxantrone and Intermediate Dose Ara-C (MIDAC) was effective, and results were similar to the use of High Dose Ara-C(HIDAC) for good risk patients(11). showed it prolongs DFS(15,16). This study was designed to describe the characteristics of adult patients with AML, evaluate the response to the available chemotherapy (in the presence of shortage and unstable supply of cytotoxic agents and antibiotics (during 2008), with follow up till the end of 2012, and to compare OS and DFS with other studies.

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Patients and methods:

From January to the end of December 2008, sixty seven patients with previously untreated AML (except M3) were admitted to the 7th floor/Medical City Teaching Hospital. Nine patients died (due to the delayed referral or old age with co-morbidities) within two weeks in spite of full supportive care, and were excluded from the study. They were followed up until the end of 2012. Diagnosis was confirmed by bone marrow examination, cytomorphology and Cytochemistry, and was classified according to French-American-British (FAB) classification).Discussion about treatment policy with the patient and family was done. Written consent was taken from all patients prior to starting chemotherapy. For patients < 60 year of age with no cardiac co-morbidity, induction with 3+7 was given which included Doxorubicin 30 mg/m2/day iv infusion over 30 min(day 1-3) and Cytosine arabinoside (ara-c) 100 mg / m2/day infusion over at least 16 h (day 1-7).For patients > 60 year of age induction with attenuated chemotherapy was given which included 2+5 regimen (the same cytotoxics and dose as in 3+7, but Doxorubicin was given for 2 days and cytosine arabinoside for 5 days) for those with no cardiamorbidity, and subcutaneous ara-c (20 mg twice daily for 10-15 days repeated every 21-28 days) taking in consideration fitness and WBC count. After receiving induction, patients were either stayed in the hospital, or discharged home. The second group of patients were < 50yr of age with no fever or bleeding at presentation, educated, live near by the hospital, and was supplied with admission paper in case of fever or bleeding, with telephone number to call on need, and to come back 10 days after discharge. Bone marrow aspirate was repeated 2-3 weeks after finishing induction if the WBC count was > 1 X109/L, otherwise if the count is less, it will be done after another week, or until the count exceed 1X109/L. A second 3+7 course was given if no CR was accomplished after the first course of chemotherapy.If CR is achieved, a consolidation with 3 monthly modified courses of MiDAC (preferred in patients under 45 yr of age) or 6 monthly courses of 2+5 regimen were given.Modified MiDAC included: Cytosine arabinoside infusion1gm/m2every 12h over 3h for 3days. and Mitaxantrone (Novantrone) iv infusion 10mg/m2/day for 3days for ½ hour, or doxorubicin 30mg/m2 infusion over ½ hour for 2days.Patients who maintained remission after consolidation were followed up monthly with CBP for 6months and then every 6 months. Any relapse during consolidation with 2+5 or with MiDAC (<45yr) were treated with salvage therapy with modified MiDAC according to patients fitness and patients preference, few salvaged with HIDAC (Cytosine arabinoside) 3gm/m2 over 3hours, twice daily on day, 1, 3, 5. If they go into CR, they were consolidated with 3 courses of the same treatment; otherwise, they were kept on oral 6 Mercaptopurine (6MP) as supportive treatment.Patients who did not achieve CR during induction were given either modified MiDAC, or 6MP as suppressive treatment.

Statistical analysis:

End points considered in the data analysis were as follows:
Complete remission rate (CR).
Overall survival (OS): calculated from the first day of diagnosis until death or last follow up.
Disease free survival (DFS): calculated from the first day of CR to relapse, death, or last follow up.
Disease free and overall survival was estimated by the Kaplan-Meier method.The statistical data were analyzed using SPSS version 18.

Results:

Fifty eight patients were eligible for the study, 28(48.3%) were male and 30(51.7) were female, with a male: female ratio of 1.07:1. Their age range 17 – 70years, with a median of 41year. 12 patients (20.6%) were above the age of 60-year.Fifty two patients (89.75%) were de novo AML, while 5(8.5%) were AML with myelodysplastic syndrome (MDS), and 1(1.75%) was therapy related (t – AML) with history of Non - Hodgkin Lymphoma.Regarding FAB classification: Mo, M1, M2, M4, M5, M6, M7 constituted 4(7%), 11(19%), 22(36%), 16(27.5%), 2(3.5%), 1(2%), 3(5%) prospectively.Twenty one patients (36.25%) presented with anaemia, while 12(20.50%), 10(17%), 5(8.75), 4(7%), 2(3.5%), 2(3.5%), 1(1.75%), 1(1.75%) presented with fever, bleeding, fever and anaemia, fever and bleeding, Lymphadenopathy, Lymphadenopathy and fever, and orbital mass respectively.The range and median results for Hb, WBC, platelets, peripheral blast and bone marrow blast were 30–110(70)gm/L, 0.8–362(38.1) X109/L, 4–120(45) X109/L), 0-93(30)%, and 20–97(60)% respectively.Forty seven patients were eligible for induction with 3+7. CR was achieved in 26 (55.3%) including 5 patients that needed 2 courses (table 1). Five (10.6%) had PR, received further induction chemotherapy with MiDAC or 2 + 5 regimen or salvaged with 6MP according to patient fitness.(one patient achieved CR with MiDAC). 16 (34%) died within 2-4 weeks because of therapy related mortality(TRM) (table 1). The cause of death was severe neutropenia in 13 and CNS bleeding in 3 patients. Death was equally distributed among patients who were kept inpatients and those discharged home after receiving induction therapy. This group has 40% 5-year OS and DFS. (Figure 1, 2)Grade 3 and 4 toxicities after 3 + 7 included haemorrhage in 4 patients (8.5%), infection 14 (30%), hepatic 5(10%), nausea and vomiting 10(21%), diarrhea 1(2%), cardiac 1(2%), neurotoxic 1(2%).Five (7.5%) patients were over 60 years with no

co-morbidity received 2+5 regimen and 6 patients (9%) were also over 60 with co-morbidity received subcutaneous cytarabine. This group had a median survival of 6-8 months with zero 5-year OS and DFS (Figure1, 2).Twenty seven patients had consolidation chemotherapy which was mainly with modified MiDAC, two with 2 + 7 and two with Novantrone + Etoposide according to availability. After consolidation 20 (74%) maintained CR, one (4%) died from sepsis secondary to severe neutropenia, 3 (11%) had relapse and were treated with Modified MiDAC or HiDAC, 1 (4%) had no response and salvaged with 6MP, while 2 (7%) lost follow up (table-4). After consolidation; Sixteen (34%) of 47patients enrolled in the study maintained CR until the end of 2012, while 4 (8.5%) relapsed and managed with supportive treatment.Five year Overall survival (OS) and disease free survival (DFS) for the whole studied patients were 30% and 34% respectively (figure 3, 4).

Table 1: Outcome of 58 patients with AML

Type of Treatment	No	%
Attenuated treatment	**11**	**19**
CR	**0**	**0**
Induction with 3 + 7	**47**	**81**
Death within 2-4 weeks	**16**	**34**
CR	**26**	**55.5**
PR	**5**	**10.5**
Consolidation	**27**	
CR	**20**	**74**
Relapse	**4**	**15**
Death	**1**	**4**
Loss follow up	**2**	**7**
Five year OS		**30**
Five Year DFS		**34**

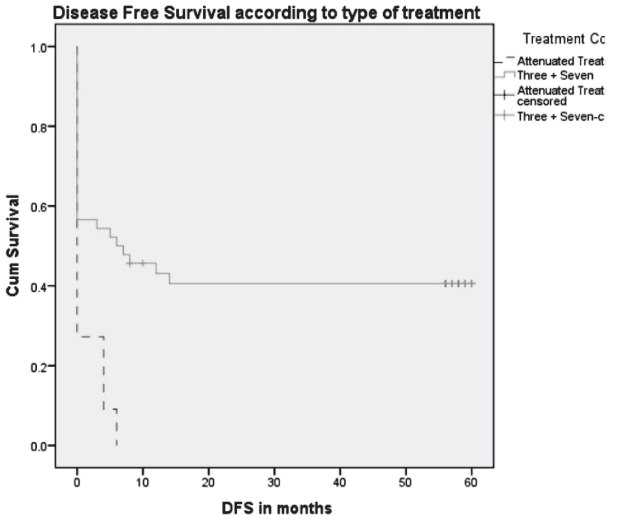

Figure 1: Kaplan-Meier DFS according to type of treatment

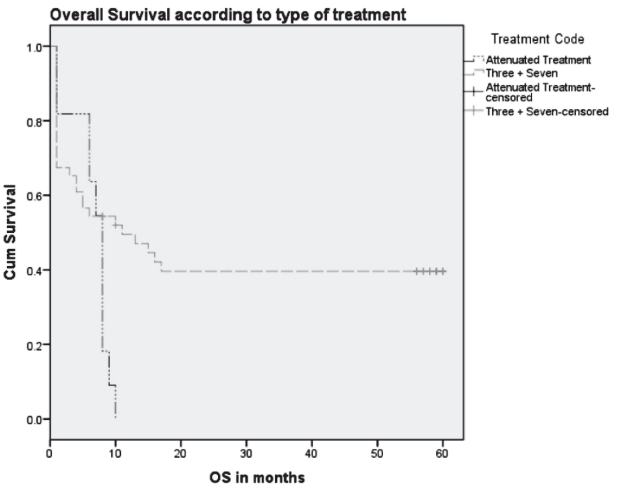

Figure 2: Kaplan-Meier OS according to type of treatment

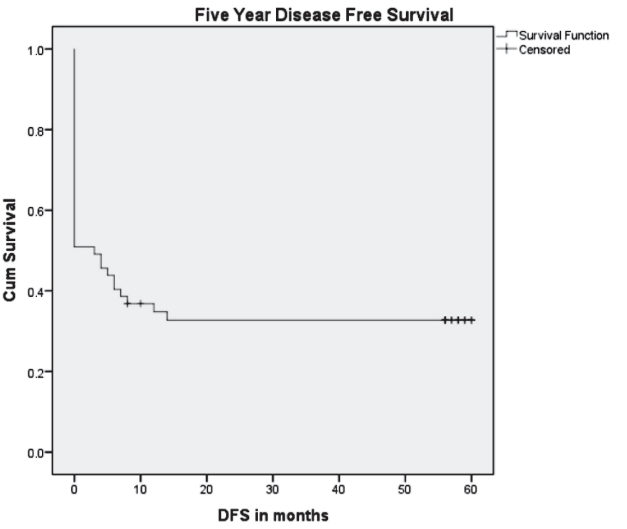

Figure 3: Kaplan Meier DFS of 58 patients with AML

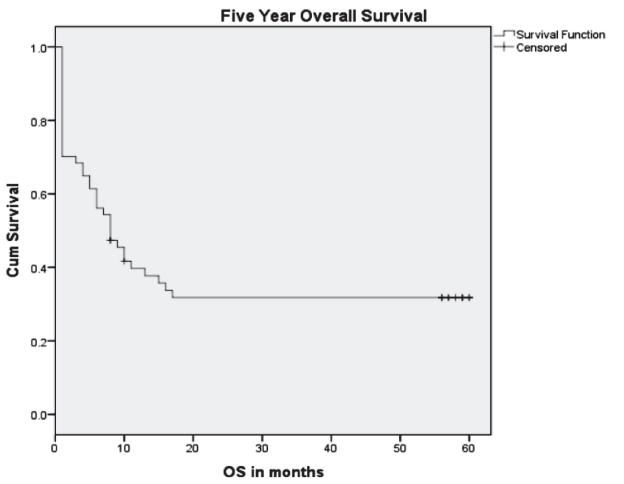

Figure 4: Kaplan-Meier OS of 58 patients with AML

Discussion:

Eleven patients (19%) were > 60-year old, median survival of this group was 6-8 months. Oberg et al studied 90 patients of same age group received daunorubicin and cytosine arabinoside with thioguanine (43 patients) or a combination in which aclarubicine was substituted for daunorubicin(47 patients), the median cause specific survival time was 178 days in the total patients group with 2, 5 and 10 year survival of 22%, 11% and 8% respectively(17). Wedding et al found that most old patients die within the first 2-years after diagnosis due to resistance or relapse of the disease or therapy related complications and small percentage can be cured(18). Thein et al found little improvement in 12 months survival over the last 3 decades which was 20% to 25% to 30% respectively and no improvement over the age of 70(19). Golvic et al concluded after studying 210 old patients managed with supportive and palliative or induction chemotherapy that only those with good ECOG PS (performance status) and HCT – CL index of ≤ 2 (comorbidity index) at presentation may be eligible for intensive chemotherapy(20).Forty seven (81%) patients were ≤ 60 year old received 3+7 induction chemotherapy regimen. CR was achieved in 26 (55.3%). This result is partially comparable to what was achieved by Niparunk(62.5%)(21), Baundaurd(81.2%)(22), Kimby(50-60%)(23), Bucher(62.7%)(24), Qachouch (62%)(25), and Parovichnikova(74.6%)(26). (Table 2)

These differences could be due to different age groups studied and different cytogenetics. Sixteen patients (34%) died within 4-8 weeks after induction, this high treatment-related mortality (TRM) can be attributed to shortage of new generation antibiotics and low yield of positive blood culture which might be due to widespread institution of antibiotics before referral, in addition to lack of laboratory facilities for fungal studies, and as mortality declines afterwards, this suggests that patients who died during this time comprise a qualitatively distinct group including performance status and age. Mortalities were equally distributed between patients that were discharged home and those who were kept inpatients after receiving induction chemotherapy. Othus et al examined 1409 patients treated on SWOG(South West Oncology Group) trials and 1942 patients at MD Anderson (MDA) from 1991-2009. 88% of the SWOG received 3+7 or regimens of similar intensity, while 92% of the MDA patients received arac-C 1.5 2gm/m2 daily for 3-5 days plus other cytotoxic agents. TRM showed a significant decrease from 18 to 3% in SWOG and 16 to 4% at MDA. The decrease was not limited to younger patients or those with a better performance status or a low WBC count(27).Five patients had PR after induction, and then were treated with MIDAC, 2+5, or salvage therapy with 6MP according to the availability of chemotherapy and general condition of the patients, one patient achieved CR and received consolidation.Toxicities secondary to induction chemotherapy were comparable to a study done by Tallman et al(28) except higher incidence of infection which was 30% compared to 12% and haemorrhage which was 4% compared to 2%, that attributed to the same causes that increased the TMR.

Twenty seven patients received consolidation chemotherapy. CR maintained in 20 patients (74%), while 4(15%) had relapse, 1(4%) died due to sepsis and 2(7%) lost follow up.Five- year OS and DFS were 30% and 34% respectively. Shubber et al reported an OS and DFS of 41%, 37% (2-year) respectively(28), Niparunk 22.2%, 41%(21), Schuichi 52.4-58.4%, 30.4-58.4%(29). Pagnano 20.5%, 34%(30), and Sperr 18.2%, 30%(31) respectively (table 3). These different results could be due to different chemotherapy regimens used, different age groups or prevalence of –ve prognostic characteristics within a study population. OS and DFS were significantly better in patients aged ≤ 60-year treated with 3+7 than those > 60 treated with attenuated regimens (2+5 or S/C cytosar) . These results indicate that age, morbidities and type of chemotherapy have significant effects on OS and DFS.

Table 2: Outcome of induction with 3 + 7 in comparison with other studies.

Reference		No of patients	Age (yrs)		CR	
			Range	Median	No	(%)
Niparunk P et al	2009(21)	96	15 – 75	43.5	60	62.5
Baundaurd M et al	1999(22)	784	> 16		663	81.2
Kimby E et al	2001(23)	139557	Unselected		50-60	
Bucher T et al	2012(24)	290	16 - 60	48	180	62
Qachouh M et al	2003(25)	98	25 - 60	32.5	58	55
Current Study		47	17 - 60	41	26	55.3

Table 3: Outcome of consolidation chemotherapy in comparison to other studies

Reference	No of patients	Age	Chemotherapy	5Y OS	5Y DFS
Shubber et al 2011(28)	26	17-45	Mod MiDAC	41(2y)	37(2yr)
Niparunk et al 2009(21)	60	15-75	Cytarabine+Anthracycline	22.2	41
Schuichi et al 2005(29)	302 296	15-64 15-64	(1)Standard courses (2)+maintenance	52.4 58.4	58.4 30.4
Pagnano et al 2000(30)	78	<60	Intensive chemo	20.5	34
Sperr et al 2004(31)	47	>60	IDAC X 1-4	18.2	30
Baudard et al 1999(22)	784	Young->60	Conventional	35.<60 60<10.6	
Current study	27	<60	Mod MiDAC, or 2+7, orN0vantrone+Etoposide	30	34

Conclusion

Early referral to the hospital is essential to avoid high mortality.Remission rate after 3+7 regimen, OS and DFS in the present study is almost similar to comparative studies. Mortality rate after induction therapy is similar among patients who were discharged home and those who were kept inpatients.Patients > 60 year age have poor OS and DFS and this need to be evaluated further.

References:

1. Yamamato JF, Coodman MT. Patterns of leukemia incidence in the United States by subtypes and demographic characteristics. 1997-2002. Cancer Causes Control 2008; 19: 379.

2. Sant M, Allemanic C, Tereanu et al. Incidence of haematological malignancy in Europe. Blood 2010; 116(19):3724.

3. Gripe LD. Adults acute leukemia. Curr Probl Cancer1997 Jan-Feb; 21 (1): 1-64.

4. Burnett AK. The treatment of acute myelogenous leukemia : Current status and novel approaches. Haematology 2005; 10, 50-53. (IVSL).

5. Larson RA. Is secondary leukemia an independent poor prognostic factor in acute myelogenous leukemia. Best Pract Res Clin Haematol. 2007 March; 20(1):29-37.

6. Meyer CA, Albitar M, Estey E, et al. Cognitive impairment, fatigue and cytokine level in patients with acute myelogenous leukemia or MDS. Cancer 2005;104:788.

7. Femandez HF, Sun Z, Yao X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myelogenous leukemia age 50 to 70 years; results of the ALFA – 9801 study. J Clin Oncol 2010 Feb; 28(5):808.

8. Lowenberg B, Ossenkopple GJ, Van Putten W, et al. High dose Daunorubicin in old Patients with acute myelogenous leukemia. N Engl J Med 2009; 361: 1235.

9. Dobner H, Estey EH, Amedori S, et al. Diagnosis and management of acute myelogenous leukemia in adults: recommendation from an international expert panel on behalf of the European Leukemia Net. Blood 2010; 115:453.

10. Rowe J, Anderson J, Cassileth j, et al. Clinical trials of adults with acute myelogenous leukemia: Experience of the Eastern Cooperativ Oncology Group in: Acute Leukemia IV: Experimental approaches and novel therapies. Berlin, Germany: Springevelag; 1994:541-546.

11. Cornelissen JJ, Van Putten WL, Verdonck LF, et al. Myeloblative HLA- identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle aged adults: benefits for whom? Results of a HOVON/SAKK donor versus no donor analysis Blood 2007; 109: 3658-3666.

12. Mandelli F, Vegna ML, Avisssati G et al. A randomized study of the efficacy of post consolidation therapy in adults non lymphoblastic leukemia: a report of the Italian Cooperative Group GIMEMA. Ann Hematol. 1992; 64: 166-172.

13. Volger WR, Weiner PS, Moore JO, et al. Long term follow up of randomized post induction therapy trial in acute non lymphoblastic leukemia (a Southern Cancer Study Group Trial). Leukemia 1995; 9: 1456-1460.

14. Rees JKH, Gray RG, Wheatly K, et al. Dose intensification in acute myeloid Leukemia: greater effectiveness at lower cost. Principle of the Medical Research Council AML 9 Study. MRC Leukemia in Adults Working Party. Br J Haematol 1996; 94: 89-98.

15. Hewlett J, Kopecky KJ, Head D, et al. A prospective evaluation of the role of allogenic marrow transplant and low dose monthly maintenance chemotherapy in the treatment of adult acute myeloid leukemia (AML), a

Southwest Oncology Group Study. Leukemia 1995; 9: 562-569.

16. Buchner J, Hiddman W, Berdel WE, et al. 6-thioguanine, cytarabine, And Daunorubicin (TAD) and high – dose cytarabine and Mitaxantrone (HAM) for induction. TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia. A randomized trial of the German AML Cooperation Group. J Clin Oncol 2003; 214: 496-504.

17. O berg G, Killander A, Bjoreman M et al. Long-term follow-up of patients > 0r 60yr old with acute myelogenous leukemia treated with intensive chemotherapy. Eur J Haematol 200 Jan; 68(6):376-81.

18. Wedding U, Hoffken K. Therapy of acute myelogenous leukemia in elderly Patients. Gerontol Geriatr 2001 Aug; 34 (4): 269-76.

19. Thein MS, Ershler WB, Jemal A, et al. Outcome of old patients with acute Myelogenous leukemia: An analysis of SEER data over three decades. Cancer 2013 Apr30. doi : 10. 1002/ cncr. 28129 (Epub ahead of print) PMID: 23633441

20. Golvic M, Golvic N, Radojkovic M, et al. Induction chemotherapy Versus palliative treatment of acute myelogenous leukemia in a consecutive cohert of elderly patients. Ann Hematol 2012; 91(9): 1363-70.

21. Niparunk P, Chuncharunee A, Ungokanont A, et al. Long term outcome of de novo acute myelogenous leukemia in thai patients. J Med Assos Thai 2009 Sept; 92(9);1143-9.

22. Baudard M, Beaucham P, Nicoud A, et al. Has the prognosis of adults with acut myelogenous leukemia improved over years?.A single institution experience of 784 patients over 16 years period. Leukemia 1999;13(10):1481-90.

23. Kimby E, Nugren P, Glimelius B, et al. A systematic overview of chemotherapy effects in acute myelogenous leukemia. Acta Oncol 2001; 40(2-3):231-52.

24. Bucher T, Gilliland DG, Rowe JM, et al. Acute myeloid leukemia (AML): different treatment strategies versus a common standard arm-combined prospective analysis by the German AML intergroup. J Clin Oncol 2012 oct 10(29):3640-50.

25. Qachouh M, Quessar A, Harif M,et al. Acute myeloblastic leukemia in adults; Evaluation of the AML 06/96 protocol. Tunis Med 2003 Jul;81(7):461-5.

26. Parovichnikova EN, Kisova GA, Sokolov AN, et al. The first result of treatment of acute myelogenous leukemia according to the AML- 01.10 protocol of the Research Group of the Haematology Centers of Russia. Ter Arkh 2012;84(7):10- 15.

27. Othus M, Kantarjian H, Petersdorf S, et al.Decling rates of Treatment-Related mortality in patients with newly diagnosed Acute Myelogenous Leukemia given intensive induction regimens: A report from SWOG and MD Anderson. Leukemia;2013 Jun 13,doi:10.1038/ leu 2013.176 (Epub ahead of print).

28. Shubber MA, Almothaffar A. The use of modified Midac regimen in the treatment of adult patients with de vovo AML in Baghdad Teaching Hospital. Iraqi Journal of Haematology 2011(vol1): 13-21.

29. Schuichi M, Hisachi S, Shigeki O, et al. Post remission comparison of four cours Of standard-dose consolidation with maintenance therapy versus three courses Of standard –dose consolidation with maintenance therapy in adults with AML. Cancer 2005; 12:2726-2734.

30. `Pagnano KB, Traina E, Takahashi T, et al.Conventional chemotherapy for Acute Myelogenous Leukemia: a Brazellian experience. Sao Paulo MJ.2000 Nov; 118(6):173-8.

31. Sperr WR, Pribauer M, Wimazal F, et al. A novel effective and safe consolidation for patients over 60 years with acute myelogenous leukemia : intermediate dose cytarabine(2x1gm/m2) on day 1,3 and 5. Clin Cancer Res 2004 Jun 15;10:3965-71.