Research Article

Outcome of 50 Iraqi Patientswith Acute Lymphoblastic Leukemia Treated by Modified German Multicenter Study Group (GMALL) Protocol

Alaa Fadhil Alwan, *FICMS (int.med.), FICMS (clin. hem)*

Date Submitted:16.04.2013
Date Accepted:16.06.2013

Address for correspondence:
Assistant professor/ the national center of hematology/ Almustansiriya University
Email: *ala_sh73@yahoo.com*

Abstract

Background and aim: Acute lymphoblastic leukemia (ALL) is a lymphoidmalignancy, which arises from bone marrow,appearing in marrow, blood circulation and otherorgans. Treatment outcome have significantly improved since the adaptation of intensification and risk adapted therapy-based on identified prognostic markers. Treatment programs in adult ALL have evolved from the successful strategies employed in pediatric ALL and incorporate multiple active agents into complex regimens. The goal of these doses intensive regimens is rapid cytoreduction with restoration of normal hematopoiesis, The aim of the study was to assess the efficacy of a modified German multicenter study group for Acute Lymphoblastic leukemia (GMALL) protocol in adult acute lymphoblastic leukemia (ALL) in respect to disease free survival (DFS) and overall survival(OS) and to determine the prognostic factors affecting this outcome.

Patients and method: A prospective study conducted in the hematology unit in Baghdad Teaching Hospital on 50 patients with newly diagnosed (ALL) between January 2006 to January 2008.A written informed consent were obtained from all patients. All patients were undergone full clinical examination with full laboratory investigations. The diagnosis based on morphology and cytochemical stains (periodic acid-Schiff, Sudan Black) of bone marrow examination. In Modified GMALL, induction phase consist of 2 phases, phase 1 induction was given over 5 weeks with weekly vincristine (VCR), Doxorubicin(DOX), and continuous oral prednisolone(RDN), Phase II induction consisted of 3 doses of weekly cyclophosphamide(CYCLO) alternating with 3 doses of weekly cytosine arabinoside (ARA-C) combined with CNS directed therapy using intrathecal Methotrexate (MTX) with daily 6-mercaptopurine(6-MP) followed by cranial irradiation. Consolidation consisted of weekly VCR and two courses of 5 days Ara-C and Etoposide (ETOP) with dexamethasone (DEXA) over a period of 4 weeks and maintenance therapy of daily 6-MP tablets and weekly MTX tablets.

Results: The study included 50 patients with median age of (28.5 years), ranged from 16-71 years. Thirty-one patients (62%) were males, while 19 patients (38%) were females. All patients received modified GMALL protocol; forty-two patients (84%) achieved complete remission (CR). The DFS and median OS were 8.5 months, 10 months respectively. The median OS at 1 year was 54%. Deaths occurred in 19 patients (38%). Infection was the main cause of death.In univariate study analysis, age less than 30 years, absence of hepatomegaly and lymphadenopathy, and peripheral blast percent less than 50% were associated with better OS while presence of lymphadenopathy was considered poor prognostic factors and associated with low CR rate, short DFS, and OS.

Conclusion: The modified GMALL protocol produced good induction remission rate but with lower survival rate in comparison to other intensive adult protocols. This study also showed that there are certain bad prognostic factors such as age more than 30 years, hepatomegaly and lymphadenopathy which adversely affect the outcome

Keywords: outcome, treatment, acute lymphoblastic leukemia.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a lymphoid malignancy, which arises from bone marrow, appearing in marrow, blood circulation and other organs[1]. Although aggressive combination chemotherapy for adult acute lymphoblastic leukemia (ALL) has improved the complete remission (CR) rates;the long-term survival of "older" adults with acute

lymphoblasticleukemia (ALL) who are intensively treated is about 40% [2-4].

Attempts to improve outcome include high doseintensification, stem cell transplantation and risk adapted therapy based on identified prognosticmarkers or minimal residual disease. However in developing countries where state funding forexpensive health care interventions is lacking, it is important that treatment modifications shouldbe cost effective [5].

The GMALL protocol study sought to improve remission duration by means of an intensive regimen in which cyclophosphamide, Ara-c, and 6-mercaptopurine were administered after the more conventional drugs for ALL, which then followed by GMALL 02/84, 03/87, 04/89 and last published trial in 2001was GMALL 05/93 in which prednisolone prophase and multiagents intensive phase are added.[6]

Although induction CR rates are 90% in many series of adult ALL, the long-term DFS over the last decade remains 25–50%, despite attempts to modify and improve post remission therapy through schedules with a variety of drugs that are active in ALL. These agents include oral and higher doses of intravenous MTX, antimetabolite such as 6-MP and 6-thioguanine, low and high-dose cytarabine, and etoposide. In addition, many of the drugs that are used during induction therapy (Anthracyclines, glucocorticoids, vincristine, and L-asparaginase) have also been reintroduced during post remission therapy.

The value of post remission dose intensification has been addressed in several large prospective clinical trials with promising results. Successive German multicenter trials have evaluated the impact of subset-specific dose intensification during post remission therapy[7].

Presumably because of its increase penetration into CNS and its long half-life, the use of dexamethasone in induction and post remission therapy appear to provide better control in the CNS and systematically than do either prednisone or prednisolone, however; one small study suggest that an increased dose of prednisolone in the context of other intensive treatment can yield result similar to those achieved with dexamethasone [8]

The aim of current study is to evaluate the outcome of treatment with modified GMALL protocolfor adult ALL patients in respect to DFS and OS and to determine the prognostic factors affecting this outcome.

PATIENTS AND METHODS

Patients

From January 2006 to January 2008, a total of 50 patients admitted to the hematology unit in Baghdad teaching hospital/ medical city were included in the study.

According to the entry criteria, patients aged ≥ 14 with the morphological and cytochemical confirmation diagnosis of All who were without prior malignancy, severe prior illness or psychiatric diseases were eligible. For all patients, a review and follow-up chart was performed to determine age, gender, residence, and duration of onset, clinical presentation, and time of diagnosis, result of investigations and follow-up of treatment.

In all patients the diagnosis of All was based on morphology of peripheral blood smear, bone marrow aspirate and biopsy using Leishman stain and cytochemical staining including periodic acid Schiff and Sudan black. Cytogenetic and molecular analyses were not performed because they were not available.

Treatment Regimens

Prior to commencing induction chemotherapy, a written consent was taken from the patient.

Available supportive measures were given to patients according to requirements.

Prophylactic platelet transfusions were given in case of thrombocytopenia below 20 x 109/L or in cases of active bleeding. Packed red blood cells were transfused to maintain the hematocrit above 24%. Patient with infections received broad spectrum antibiotics.

Hyperuricemia and other electrolytes disturbances were corrected when present. The drugs and doses used in modified GMALL protocol is listed in table 1.

Table 1. Modified GMALL protocol

Drug	Dose	Days
Induction Phase1		
Prednisone (oral)	40 mg/m^2	1-28
Vincristine (lV push)	1.4 mg/m^2(max.2 mg)	1,8,15,22,29
Doxorubicin(IV infusion)	30 mg/m^2	1,8,15,22,29
Phase 2		
Cyclophosphamide (IV infusion/ 1 hr.)	650 mg/m^2 (max.1gm)	36,50,64
Cytosine arabinoside (IV infusion/3 hrs.)	250 mg/m^2 (max.500mg)	43,57,71
6-mercaptopurine(oral)	60mg/m^2	36-71
Methotrexate (IT)	12.5mg/m^2	36,43,50, 57, 64
Consolidation		
Dexamethasone (oral)	10 mg/m^2	1-28
Vincristine (IV push)	1.4 mg/m^2(max.2 mg)	1, 8, 15, 22
Cytosine arabinoside (IV infusion/1 hr.)	75 mg/m^2	1-5, 24-28
Etoposide(Infusion/1 hr.)	100mg/m^2	1-5 , 24-28
Maintenance		
6-mercaptopurine (P0)	60 mg/m^2	Daily
Methotrexate (PO, IM,IV)	20 mg/m^2	Weekly
Pulse therapy every 12 weeks		
Vincristine (IV push)	1.4mg/m^2(max.2 mg)	Day 1, 8
Doxorubicin (IV infusion)	30 mg/m^2	Day 1, 8
Methotrexate (IT)	12.5mg/m^2	Day 1
Prednisone (oral)	40 mg/m^2	For 14 days

The differences from the original GMALL protocol are: phaseI induction is given over 5 week instead of 4 week, L-asparaginase is omitted from phase I induction. A 6-mercaptopurine tablet is used instead of 6- thioguanine during Phase II induction and consolidation. Response criteria: Bone marrow aspiration and biopsy were performed at the end of the induction phase. Patients were considered to be in CR when WBC more than 3 x 10^9 /L with absolute neutrophils count was more than 1 x 10^9/ L, the platelet count was higher than 100 x 10^9/ L, the bone marrow morphology was normal with less than 5% blasts, there was no evidence of extramedullary leukemia, and resolution of organomegaly. Patients who passed into CR had given consolidation according to above protocols.

Those failing induction chemotherapy were considered as failures or resistant cases. Relapse was defined as recurrence of lymphoblasts or localized leukemic infiltrate at any site after patient entered into CR.

Statistical analysis: Patients' data were tabulated and processed using SPSS 15 (Statistical package for social sciences) for windows. Qualitative data are expressed as frequency and percentage, quantitative data as mean and median. Chi square and T-test were used to identify the association between different parameters. Kaplan-Meier methods were used to estimate the survival curves. P values $\leq$ 0.05 were considered significant. Overall survival (OS) was defined as time from date of initiation of treatment till death or date of last follow up. Disease free survival (DFS) was defined as time from achieving CR to relapse, or death from any cause or date of last follow up.

RESULTS

Characteristics of patients:

The clinical and hematological characteristics at diagnosis of the fifty patients included in this study are summarized in table (2), there were 31 males and 19 females with median age of 28.5 years (range: 16–71 years). All patients were treated with modified GMALL with median follow-up of 9.5 months (range 1-30 months).

Table 2. clinical and haematological characteristics of 50 ALL patients at time of presentation

Characteristic	No. of patient (%)
No. of pt. (%)	50 (100)
Mean Age (years)	28.5
Gender male	31(62)
female	19(38)
Lymphadenopathy present	14(28)
absent	36(72)
Splenomegaly present	26(52)
absent	24(48)
Hepatomegaly present	10(20)
absent	40(80)
Haemoglobin g/dl <10	35(70)
≥10	15(30)
WBC (x10^9/ L) <30	32(64)
≥30	18(36)
Platelets(x10^9/l) <50	37(74)
≥50	13(26)
Peripheral blood Blasts%	
<50%	25(50)
≥50%	25(50)

Outcome of Therapy:

Out of 50 patients who were treated with modified GMALL, 42 patients (84%) achieved CR. one patient died during induction and 7 patients (14%) were

resistant to induction. Relapse occurred in 18 patients (43%), 8 patients during consolidation and 10 patients during maintenance. The 1 year CR was 36% and at 2 year 31%. The median DFS and median OS at 1 year for modified GMALL group were 8.5 months, 10 months respectively. Table (3) compare between the CR rate of different parameters used in the study according to the clinical and hematological characteristics of patients at presentation. There was no significance impact ofage, sex, Hb level, WBC count, platelets count, peripheral blast count, splenomegaly, and hepatomegaly on the CR rate. The only clinical parameter affecting CR rate was presence of lymphadenopath.

Table 3. relationship of clinical and hematological characteristics at presentation with CR rate.

Characteristics	CR %	P value
Age ≥ 30 yrs. <30 yrs.	81 85	NS
Gender male Female	84 84	NS
Hb < 10 g/dL ≥ 10 g/dL	86 80	NS
WBC ≥30(x 10^9/L) <30 (x 10^9/L)	72 90	NS
Platelets ≥50(x10^9/L) <50(x 10^9/L)	92 81	NS
Splenomegaly present absent	77 92	NS
Hepatomegaly present absent	60 90	NS
Lymphadenopathy present absent	 43 100	0.002
Peripheral blood blasts ≥ 50% < 50%	 80 88	NS

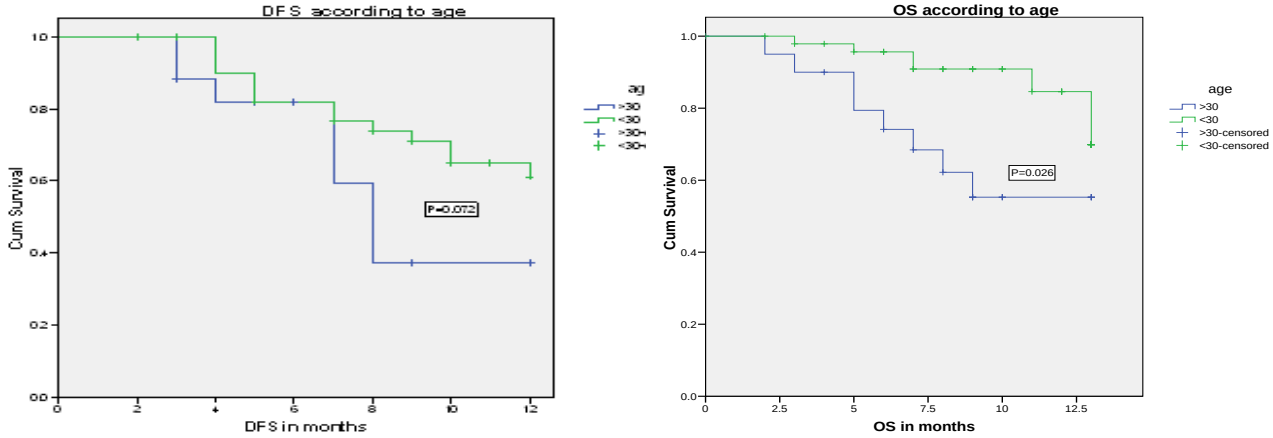
Table (4) shows the relationship of prognostic parameters with the median DFS and OS. There was a significant relationship between age with median OS where patient< 30 yearhad better OS. There was no significant association of age with DFS. Sex, hemoglobin level, and platelets count had no significant impact on either DFS or OS. The DFS and OS were significantly affected by WBC count. They are better when the count < 30 x 109 /L. DFS and OS were negatively influence by presence of lymphadenopathy with the median DFS and OS at 1year was 17%, 15% respectively (p 0.000). Regarding peripheral blast percent, blasts< 50% is associated with better OS than blasts ≥ 50%.

Table 4. Prognostic factors for overall survival and disease-free survival (Univariate analysis)

Characteristics	Median DFS month (% at 1 year)	P value	Median OS month (% at 1 year)	P value
Age ≥ 30 yrs. <30 yrs.	7 (34) 10(55)	NS	6.5(41) 13(61)	0.012
Gender male Female	7.5 (42) 10.5 (39)	0.05	10 (51) 9 (52)	NS
Hb ≥ 10 g/dL < 10 g/dL	7.5(57) 9(59)	NS	9(42) 10(57)	NS
WBC(x 10^9/l) ≥30 <30	7(40) 9(52)	0.032	7.5(52) 11.5(40)	0.036
Platelets(x10^9/) ≥50 <50	7.5(47) 9(51)	NS	9(62) 10(50)	NS
Splenomegaly present Absent	9(40) 8(57)	NS	10(41) 10(69)	0.043
Hepatomegaly present absent	7.5(43) 9 (53)	NS	8 (45) 11.5(59)	NS
Lymphadenopathy Present Absent	 4(17) 9(57)	0.001	 6.5(15) 12.5(70)	0.000
Peripheral blasts ≥ 50% < 50%	7.5(39) 9(59)	NS	8(38) 13(68)	0.019

NS: Not Significant

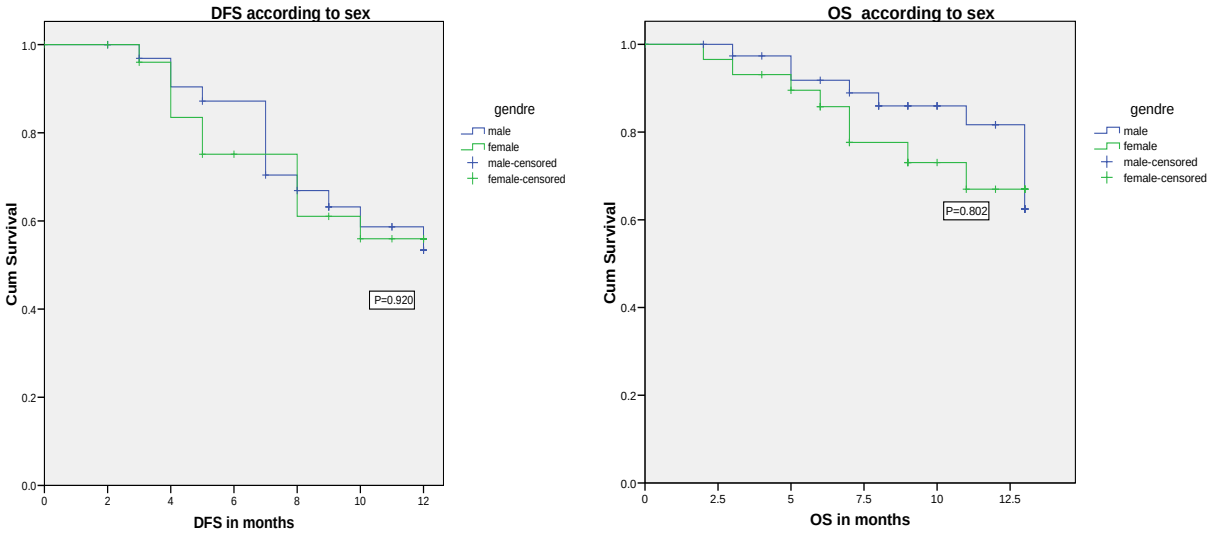
Fig 1 and 2 shows the survival function for the modified GMALL according to age and sex with probable estimate at 1 year



(a) DFS according to age (P value not significant)

(b) OS according to age (P value significant)

Fig 1. Kaplan-Meier estimate at 1 year



(a) DFS according to sex (P value not significant) **(b)** OS according to sex (P value significant)

Fig 2. Kaplan-Meier estimate at 1 year

DISCUSSION

The results of intensive treatment in adult All have been extensively studied [7, 9-11], and a variety of clinical and hematological parameters that could influence the achievement of CR have been reported [12-14]. The goal of this study was to evaluate GMALL protocol which was used in our daily practice in respect to treatment outcome and DFS and OS.

Regarding pre-treatment characteristics this study showed that the median age were 28.5 years which indicate that majority of patients were below 30 year, same results were reported by Ali M Jawad et al, Annino et al, kantarjian et al [11,12,14], which is a favorable prognostic factors but the difference was statistically not significant. Males were more common than female which is similar to that reported by other studies[11,13,and14]; again the difference was not significant.

No significant differences were found in other pre-treatment characteristics apart from hepatomegaly which was exclusively presented in all patients (p=0.031) and lymphadenopathy which was also predominant (p=0.034) these are of the poor prognostic parameters which may hasten relapse after achieving CR. Regarding treatment outcome, the CR rate was 84%, this result is equal to or higher than that reported in previous contemporary studies of adult All[11-14,16] .Regarding induction failure; eight patients (16%) failed to respond to induction chemotherapy including 1 patient death, which may be due to lack of adherence of patient to with 5weeks interval induction protocol which is similar to that found by Bajel et al[10].

Due to intensification regimen with Ara-C and Cyclophosphamide which followed by high dose MTX and 4 consolidation courses, relapse rate were lower in other study than in this study (26%versus 43% respectively) at 2 year follow-up[12].

Types of relapses were mainly hematological relapse occurred in 14 patients (78%) in this study, most of them occurred due to poor compliance or the patient refuses to continue treatment while four patients (22%) got isolated CNS relapse ,which is higher than that reported in other studies[17,18], which reflect that better protection to CNS is done by using high dose MTX after induction and intrathecal chemotherapy at different period of consolidation.

Nineteen patient (38%) died in this study, the main cause of death in this study was infection 84% which reflected lack of supportive care, negligence of preventive measures and laxity in treatment of infection, in addition to delay in referral of some cases which made the patient presented with advanced stage of disease, besides that poor compliance and adherence to chemotherapy.

After median follow-up of 10 months(range 1-30 months) for patients, the 1 year DFS was 49% and OS was 54% and the 2 year DFS and OS was (44%), (40%) respectively , others reported lower results but with follow-up range from 3 years to 10 years [2,11,14].

In this study, age had a significant impact on survival with 1 year OS of 61% for patients < 30 years, 41% for patients>30 years(p= 0.012) while for the 1 year DFS , age had no significant impact, this result was similar to studies by Bajel et al and Annino et al[10,11].

Age less than or more than 30 years had no significant relation with CR rate in contrast to that found by Sive et al who reported that age > 30 years had a significantly better CR than those below 30 years which is not in line of many contemporary studies. [18] Gender was an independent prognostic factor for CR and survival in different studies[17] but, the present study failed to demonstrate a relationship, as there was no significant association between sex and CR rate, DFS and OS. Presence of lymphadenopathy, splenomegaly and hepatomegaly was associated with poor outcome in respect to CR rate and DFS and OS with no superiority of one protocol over the other and this finding is consistent with previous studies of adult All[13,15,19].

Regarding hematological characteristic at presentation various trials had confirmed that initial high WBC count > 30 x109 /L was associated with poor outcome and short survival[12,13,14,15,19], it was even considered as the most deleterious prognostic factor in All with OS of 1-29% but in this study WBC count did not influence the CR rate , even though, patients with WBC count of more than 30 $x10^9$/L had shorter CR duration , DFS , and OS than did patient with less than 30 $x10^9$/L, this difference was not statistically significant. A lack of prognostic value for WBC count was reported also by Bajel et al[10].

In this study patients who presented with hepatomegaly and lymphadenopathy had lower CR, and short OS rate than the rest of patient, this was statistically significant (p=0.002) and (0.000) respectively and this is similar to that found by Hoelzer et al [8] and Annino et al [11] whilesplenomegaly was found in 52% of patients but it has no significant impact on CR rate, DFS or OS.

CONCLUSIONS

The modified GMALL protocol produced good induction remission rate but a lower survival rate in comparison to other intensive adult protocols. However, this studyhas several limitations including the small number of patients,and the relatively short follow-upduration. Therefore, further studies with a longer follow-upand randomized study design are needed to confirm the benefit on OS and DFS.

This study also showed that there are certain bad prognostic factors such as age more than 30 years, hepatomegaly and lymphadenopathy which adversely affect the outcome.

REFERENCES

1. Mohammad AM, Mohhamad MK, Mehdi M.Outcome of Adult Acute Lymphoblastic Leukemia inSouth East of Iran (Zahedan).***Iran J Cancer Prev*** 2012; 5(3):130-137
2. David I. Marks1 .Treating the "Older" Adult with Acute LymphoblasticLeukemia. ***ASH Education Book December 4***, 2010 vol. 2010 no. 1 13-20
3. Hoelzer D, Gokbuget N. New approaches to acute lymphoblastic leukemia in adults: where do we go? ***SeminOncol*** 2000; 27: 540-59
4. Chandy M. Childhood acute lymphoblastic leukemia in India: an approach to management in a three-tier society. ***Med PediatrOncol***. 1995 Sep; 25(3):197-203.
5. Hoelzer DF. Diagnosis and treatment of adult ALL. In: Wiernik PH, CanellosGP, KyleRA eds. neoplastic diseases of the blood3rd edition.***New York*** 1996:295
6. Ludwig W-D: Immunophenotypic and genotypic features, clinical characteristics, and treatment outcome of adult pro-B acute lymphoblastic leukemia: results of the German Multicenter Trials GMALL 03/87 and 04/89. ***Blood***1998; 92:1898
7. Pui C H, Evans W E. Treatment of acute lymphoblastic Leukemia. N Eng. ***J Med*** 2006; 354:166-175
8. Hoelzer D, Gokbuget N, Digel W, et al. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. ***Blood*** 2002; 99:4379–4385
9. Cimino G: Clinico-biologic features and treatment outcome of adult pro-B-ALL patients enrolled in the GIMEMA 0496 study: absence of the ALL1/AF4 and of the BCR/ABL fusion genes correlates with a significantly better clinical outcome. ***Blood***2003; 102:2014
10. Bajel A, George B, Mathews V et al. Adult ALL: treatment outcome and prognostic factors in an Indian population using a modified German ALL (GMALL) Protocol. ***Leukemia*** 2007; 21 22 30-33:
11. Annino L, Vegna ML, Camera A, Specchia G, Visani G, FioritoniG,Ferrara F, Peta A, Ciolli S, Deplano W, Fabbiano F, Sica S, Di Raimondo F, Cascavilla N, Tabilio A, Leoni P, Invernizzi R, Baccarani M, Rotoli B, Amadori S, Mandelli F. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. ***Blood*** 2002; 99: 863-71.
12. Ali M Jawad, Batool A GhYassin. Adult ALL criteria of patients with failed initial induction chemotherapy. ***J Fac Med Baghdad*** 2003; vol 45, no.3-4:260-63
13. Thomas X, Boiron JM, Huguet F et al. Outcome of treatment in adult with ALL: analysis of the LALA-94 trail. ***J ClicOncol*** 2004; 22: 4075-86
14. Karantijian H, Thomas D, O Brien S et al. long term follow up of results of hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone(hyper-CVAD), a dose intensive regimen in adult with acute ALL. ***Cancer*** 2004; 101:2788-801
15. Rowe JM, Goldstone AH. How I treat acute lymphoblastic leukemia. ***Blood***2007; 110:2268-75

16. Rowe JM, Buck G, Burnett AK et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALLXII/ECOG E2993.***blood*** 2005; 106:3760-3766

17. Pui CH. Central nervous system disease in ALL: prophylaxis and treatment. Hematology Am SocHematol .***Educational Program*** 2006:142-144

18. Sive JI, Buck G, Fielding A, Lazarus HM, Litzow MR, Luger S, Marks DI, McMillan A, Moorman AV, Richards SM, Rowe JM, Tallman MS, Goldstone AH. Outcomes in older adults with acute lymphoblastic leukemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. ***Br J Haematol***. 2012 May; 157(4):463-71

19. Gokbuget N, Arnold R, Buechner T. intensification of induction and consolidation improve only subgroup of adult ALL: analysis of 1200 patient in GMALL study 05/93.***blood*** 2001; 98: abstract# 80