Total Parenteral Nutrition and Decreased Dose Idarubicin Based Treatment of Acute Myeloid Leukemia During Childhood

İbrahim Bayram[1], Fatih Erbey[1], Mustafa Kömür[2], Atila Tanyeli[1]

Çukurova University, Medical Faculty, Departments of Pediatric Oncology[1] and Pediatrics[2], Adana, Turkey

Eur J Gen Med 2010;7(3):282-287

Received: 01.10.2009

Accepted: 02.05.2010

***Correspondence**: Dr. İbrahim Bayram, Cukurova University Medical Faculty, Division of Pediatric Oncology, Adana, Turkey, Fax: 03223387444, Tel: 03223387444, 03223386060/3116.*
E-mail: mrbairam@cu.edu.tr, dribrahimbayram@windowslive.com

ABSTRACT

***Aim**: Disease free survival rate for acute myeloid leukemia (AML) is still below 50% for the last 30 years. Our objective was to compare the results of two different dosages of idarubicin (12 mg/m2 versus 8 mg/m2) therapy for newly diagnosed AML patients.*

***Method**: Sixty eight patients with AML were treated between February, 1998 and January, 2005. We designed two therapy groups comprising of 12 mg/m2/day idarubicin therapy (group I), 8 mg/m2/day idarubicin therapy and when oral nutrition is broken, we have given parenteral nutrition (group II). Overall survival (OS), event free survival (EFS), disease free survival (DFS) data were assessed and other tests were performed when needed.*

***Result**: There were 26 patients (38.2%) in group I and 42 patients (61.8%) in group II. After the first induction therapy, 20 patients (76.9%) in group I and 36 in group II (85.7%) had CR or partial remission. After two courses of induction, treatment-related mortality (TRM) was 34.6% in group I and 7.1% in group II (p: 0.006). OS of the patients in group I/II were 44/81% for 12 months, 34/54% for 24 months, 29/48% for 36 months. EFS were 43/65% for 12 months, 34/50% for 24 months, and 29/50% for 36 months. OS and DFS rates were statistically significant but EFS rates were not, in group I and II.*

***Conclusion**: The protocol with idarubicin dose of 8 mg/m2/day has less TRM in comparison to that of 12 mg/m2/day and has better OS and EFS.*

***Key words**: AML, leukemia, nutrition, parenteral nutrition, childhood, idarubicin.*

Çocukluk Çağındaki Akut Myeloid Lösemi Tedavisinde Azaltılmış Doz İdarubisin ve Parenteral Beslenme Tedavisi

Amaç: *Akut myeloid lösemi (AML) hastalığı için sağkalım oranı, son 30 yıldır % 50'nin hala altındadır. Amacımız, idarubicinin iki farklı dozları ile tedavi edilen (12 mg/m2 karşı 8 mg/m2) yeni tanı AML hastalarının sonuçları karşılaştırmaktır.*
Metod: *Altmış sekiz AML hastası Şubat 1998 ve Ocak 2005 tarihleri arasında tedavi edildi. İki tedavi grubu; idarubicin tedavisi 12 mg/m2/gün (grup I), 8 mg/m2/gün ve oral beslenme bozulduğunda parenteral beslenme verilen hastalar (grup II) olarak şekillendirildi. Genel sağkalım (OS), olaysız sağkalım (EFS), hastalıksız sağkalım (DFS) verileri değerlendirildi ve diğer testler gerektiğinde yapıldı.*
Bulgular: *Grup I'de 26 hasta (% 38.2) ve grup II'de 42 hasta (% 61.8) vardı. İlk tedavi kürü sonrası grup I'deki hastaların 20'sinde (% 76.9), grup II'deki hastaların ise 36'sında (% 85.7) tam ya da kısmi düzelme vardı. İki kür sonra, tedaviye bağlı mortalite (TRM) grup I'de % 34.6 ve grup II'de ise % 7.1 idi (p: 0.006). OS grup I/II hastalarda 12 ay, 24 ay, 36 ay için sırasıyla % 29/48, %34/54 ve % 44/81 olduğu saptandı. EFS 12 ay, 24 ay için %34/50 için 43/65 ve% 29/50% 36 ay idi. Grup I ve II için OS ve DFS oranları istatistiksel olarak anlamlı, fakat EFS oranı için anlamlı değildi.*
Sonuç: *İdarubisinin 8 mg/m2/gün dozu verilen protokolü, 12 mg/m2/gün doz verilen protokole göre daha az tedavi ilişkili mortalite olduğu ve OS ve EFS oranlarının daha iyi olduğu saptandı.*
Anahtar kelimeler: *AML, lösemi, beslenme, parenteral beslenme, çocukluk çağı, idarubisin.*

INTRODUCTION

Although there have been lots of important improvements in the treatment of acute myeloid leukemia (AML) during the past 30 years, disease free survival rate is still below 50%. Mortalities are induced by the progress of the disease due to the resistance to chemotherapeutics and the complications of the treatment (1). The complete remission (CR) rate of 38 patients treated in our clinic [idarubicin 12 mg/m2 (3 days)] between 1992 and 1999 was 71%, and overall survival (OS) for 12 months was 40% and for 36 months was 23% (2). In this study we observed that most of the patients died during the first year and many prior to the first two induction treatments due to infections arising from acute mucositis and extended myelotixicity. That is why we decided to decrease severe infections due to mucositis and myelotoxicity that are secondary to chemotherapy. In order to do this we first decreased the idarubicin dose from 12 to 8 mg/m2/day and secondly started parenteral nutrition on patients the oral intake of which had decreased. In this study, our aim was to compare the results of two different dosage of idarubicin (12 mg/m2 versus 8 mg/m2) therapy for newly diagnosed AML (FAB classification) patients.

MATERIALS AND METHODS

The study included 68 patients with AML treated between February, 1998 and January, 2005. Morphological assessment was performed according to French-American-British (FAB) classification. Leukemia diagnosis was performed in the patients who had blast over 30% in their bone marrow aspiration samples. Bone marrow samples were stained with Wright-Giemsa, PAS, Sudan black and esterase stainings. Hepatomegaly, splenomegaly, lymphadenopathy and bleeding detected in the physical examination of all patients were recorded. Routine blood counts were also performed. Liver and renal function tests, flow cytometric examination, monoclonal antibodies and OS, event-free survival (EFS), disease free survival (DFS) were assessed. If blast rate was below 5% in the bone marrow, complete remission and if that was between 5-20%, partial remission was determined. The drugs used in the treatment of AML on group I is shown in Table 1. For Group II, the dosage of idarubicin (8 mg/m2/day, 3 doses) was reduced at induction phase I-II and TPN was begun.

This study was prospective and has been approved by the local ethics committee and written informed consent of all parents were taken.

Statistics tests

Statistical analyses were performed by SPSS 10.0 pack program. Chi-square and Kaplan Meier tests were applied for the evaluation of the data. $p \leq 0.05$ was considered as statistically significant.

RESULTS

Out of 68 cases involved in the study groups, 35 (51.5%) were male and 33 (48.5%) were female. The mean age

***Table 1**. Using drugs in treatment of group I and II*

Induction phase-I and II (every 3 weeks)	*Consolidation phase I*	*Consolidation phase II*	*Maintenance therapy*
***Cytosine arabinoside**; 100 mg/m2 every 12 hr for 30 minutes (iv), 14 doses,* ***Idarubicin**: 8-12 mg/m2/day, 0-2 days (iv), 3 doses,* ***VP-16**: 100 mg/m2/day for 60 minutes (iv), 3-5 days, 3 doses,* ***Cystosine arabinoside (Intrathecal)**: Day 0*	***Cytosine arabinoside**: 3 gr/m2 every 12 hr for 4 hours (iv), 0-1 days, 4 doses,* ***L-Asparaginase**: 6000 U/m2 (im) at 42nd hour,* ***Methotrexate (intrathecal)**: Day 0*	***Idarubicin**: 8-12 mg/m2/day, 0-1 days (iv), 2 doses,* ***Cytosine arabinoside**: 200 mg/m2/dose for continuous infusion, 1-5 days, 5 doses,* ***VP-16** : 100 mg/m2/day for 60 minutes (iv), 1-5 days, 5 doses,* ***Methotrexate (intrathecal)**: Day 0*	***6-Thioguanine**: 75 mg/m2/day p.o., 0-27 days,* ***Vincristine**: 1.5 mg/m2 iv, day 0,* ***Cytosine arabinoside**: 75 mg/m2/day iv, 0-3 days,* ***Cyclophosphamide**: 75 mg/m2/day iv, 0-3 days.* *Note: Maintenance therapy is repeated every 30 days, given for 12 cycles*

***Tablo 2**. Complications during AML treatment*

Complications	*Induction phase I*		*Induction phase II*		*Consolidation phase I-II*		*Maintenance*	
	GroupI	*GroupII*	*GroupI*	*GroupII*	*GroupI*	*GroupII*	*GroupI*	*GroupII*
	n %	*n %*	*n %*	*n %*	*n %*	*n %*	*n %*	*n %*
Neutropenia	*26/100*	*42/100*	*17/85*	*33/82.5*	*12/80*		*3/27.3*	
Febrile neutropenia	*23 / 88.5*	*38/90.5*	*13/65*	*24/60*	*6/40*	*17/50*	*2/18.2*	*5/16.1*
Mucositis	*20 / 76.9*	*16/38.1*	*6/30*	*15/37.5*	*4/26.6*	*6/17.7*	*5/16.1*	
Pulmonary i.	*5 / 19.2*	*11/26.2*	*4/25*	*4/10*	*3/20*	*3/8.8*	*1/9.1*	*3/9.7*
Gastroenteritis	*5 / 19.2*	*15/35.1*	*3/15*	*8/20*	*2/13.3*	*4/11.8*	*3/27.3*	*3/9.7*
Abscess	*2 / 7.8*	*3/7.1*	*1/5*	*4/10*	*1/6.6*			
Urinary i.	*3 / 11.5*		*1/5*	*4/10*	*2/5.9*		*1/3.2*	
Upper respiratory i.	*2 / 7.8*	*1/2.4*	*1/5*	*2/5*	*1/6.6*	*4/11.8*	*5/45.5*	*6/19.4*
Bleeding	*2 / 7.8*	*4/9.5*	*3/15*	*1/2.5*	*1/6.6*		*2/18.2*	
Coagulopathy, hepatitis	*4 / 15.4*	*5/11.9*	*1/5*		*1/6.6*			
Cardiac failure	*1 / 3.8*	*2/4.8*						
Anal lesions	*3 / 11.5*	*5/11.9*	*2/10*		*2/5.9*			
Menengitis	*(-)*		*1/5*					
Sepsis	*4 / 15.4*	*2/4.8*	*1/5*	*1/2.5*	*1/6.6*	*3/8.8*	*1/3.2*	
CNS involvement		*1/2.4*						
Thrombosis				*1/2.5*				
Chicken pox								*1/3.2*
Total patient *n*	*26*	*42*	*20*	*40*	*15*	*34*	*11*	*31*
%	*100*	*100*	*76.9*	*95.2*	*57.7*	*81.0*	*42.3*	*73.8*

was 85.3±46.9 months (range 6-168 months). There were 26 patients (38.2%) in group I and 42 (61.8%), in group II. The complications that occurred during therapy can be seen in Table 2. These complications were mostly seen during induction phase I. The complications were relatively less during the other phases. In induction and consolidation phases including intensive therapies; neutropenia, febrile neutropenia and mucositis were the most common complications. The most common complication was respiratory tract infection and the second was neutropenia during the maintenance therapy. After the first induction therapy of patients in group I, complete remission (CR) was achieved in 16 patients (61.5 %) and partial remission (PR), in 4 patients (15.4%). Six cases (23.1%) had died due to the complications during therapy. Total (CR+PR) remission rate was 76.9%. Seven patients (26.9%) completed chemotherapy protocole and they were followed without chemotherapy (17-63 month) after maintenance. For one of the patients secondary aplasia developed and he died due to the infectious complication at the 17th month without chemotherapy. As a result, 6 cases (23.1%) are being

Table3. Prognosis of patient with AML

	Induction		Consolidation				
	phase I	phase II	phase I	phase II	Maintenance	Terminated of treatment	Results
Group I, n(%)	26 (100)	20 (76.9)	17(65.4)		11 (42.3)		
Group II, n(%)	42 (100)	35 (83.3)	34 (81)		30 (71.5)		
Died cases							
Group I, n(%)	6 (23.1)	3 (11.5)	3 (11.5)			1 (3.9)	16 (61.5)
GroupII, n(%)	2 (4.8)	1 (2.4)	2 (4.8)				14 (33.3)
Follow up							
Complete remission							
Group I, n(%)	16 (61.5)	13 (50)	11 (42.3)		7 (26.9)	6 (23.1)	6 (23.1)
GroupII, n(%)	33 (78.6)	34 (81)	30 (71.5)		23 (54.8)	11 (26.2)	23 (54.8)
Out of follow							
Group I n(%)	(-)	2 (7.7)	2 (7.7)		(-)	(-)	4 (15.4)
Group II n(%)		3 (7.1)	2 (4.8)				5 (11.9)

followed up by our clinic, 16 cases (61.5%) died and 4 cases (15.4%) are not followed up (Table 3). Of the patients in group II (42 cases), CR was achieved in 33 cases (78.6%) and PR was achieved in 3 patients (7.1%) after the first induction therapy. No remission was obtained in 4 patients (9.5%). Two patients died due to complications developed during the therapy. Total (CR+PR) remission rate was 85.7% (36 cases). After continuing chemotherapy, 23 cases (54.8%) has been followed up in our clinic [11 cases (26.2%) are without chemotherapy (2-24 months)], 14 cases (33.3%) died and 5, were out of our follow-up (Table 3). The relapse rate of group I and group II were 26.9% (7 cases) and 38.1% (16 cases), respectively. The difference between these two groups were not statistically significant (p=0.2) (Table 4). After two courses of induction, treatment-related mortality (TRM) was 34.6% and 7.1% respectively for groups I and II. These results were determined to be statistically significant (Chi-square, p= 0.006). We have seen that OS of the patients in group I/group II were 44/81%

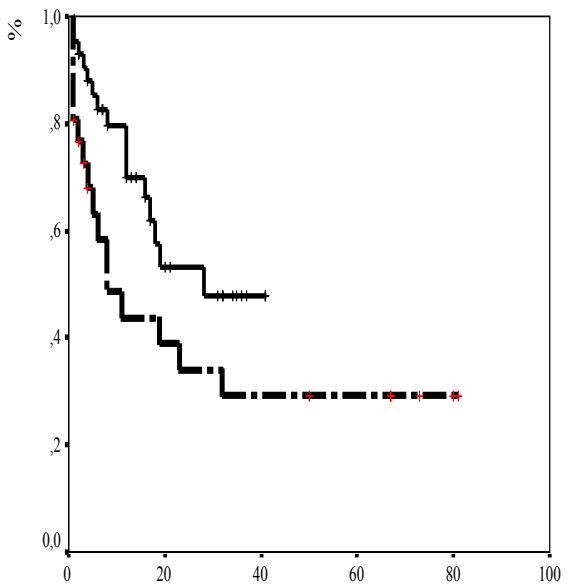

Figure 1: OS of Group I and II, Months (Kaplan-Meier Test)

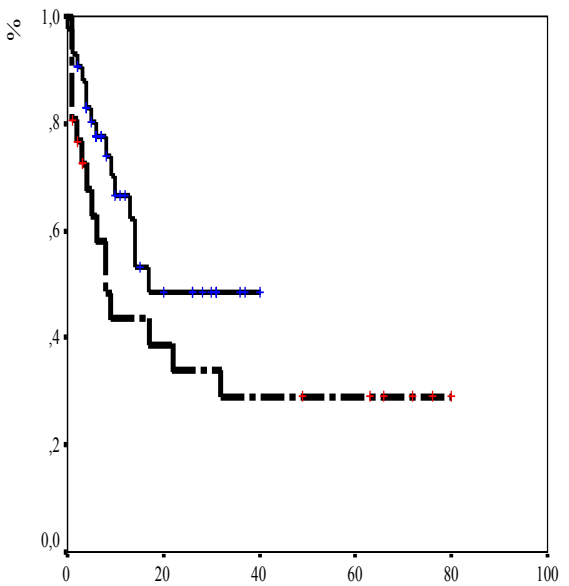

Figure 2: EFS of Group I and II, Months (Kaplan-Meier Test)

Table 4. *Prognosis of relapse cases, n(%)*

	Group I	Group II
Relapse Cases	*7(26.9)*	*16(38.1)*
follow up		
Complete remission	*(-)*	*3(18.8)*
Again Relapse cases	*(-)*	*2(12.5)*
Refractory cases	*(-)*	*1(6.3)*
Results		
Alive cases	*(-)*	*5(71.4)*
Died cases	*2(28.6)*	*6(37.5)*
Out of follow	*7(43.8)*	*3(18.8)*

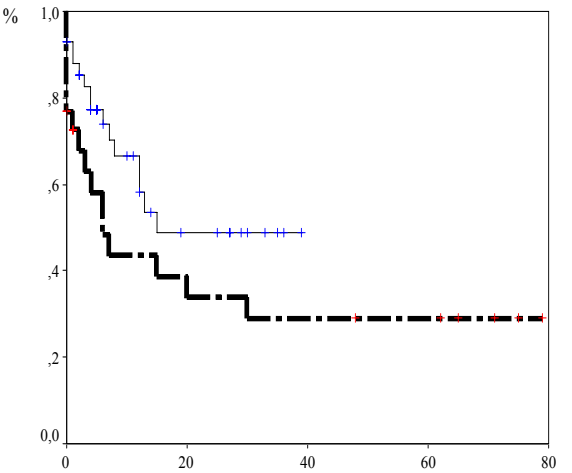

Figure 3: DFS of Group I and II, Months (Kaplan-Meier Test)

for 12 months, 34/54% for 24 months, 29/48% for 36 months. EFS were 43/65% for 12 months, 34/50% for 24 months, and 29/50% for 36 months. DFS were 44/62% for 12 months, 34/51% for 24 months, and 29/51% for 36 months (Figure 1-3). When survival rates were compared between two groups, the difference of OS and DFS rates were statistically significant (Breslow, Tarone-Ware), but the difference of EFS rates were not statistically significant.

DISCUSSION

Many patients with AML had died during intensive induction therapy. Idarubicin 12 mg/m2/day, 3 doses was changed to 8 mg/m2/day, 3 doses. Our aim was to reduce deep neutropenia and serious infections during the first treatment, and reduce infectious complications, and treat the AML. It is reported that relapse developed in 30-40% of newly diagnosed children with AML. The prognosis of patients who had developed relapse in 18 months were worse than the patients who were newly diagnosed, and also they had shorter remissions than those who were newly diagnosed (3-8). Relapse had developed approximately after the first year in the patients that we followed up in our clinic and then their induction phase I treatments were modified. As we could not manage these relapsing patients to enter remission, they began to die. That's why we have to take precautions for these patients in order to prevent relapse. Because it is very difficult for patients that develop relapse to enter into remission again. Damon et al. (9) reported that the CR rate was 51% in 138 AML patients and TRM rate was 11%. Virchis et al. (10) applied fludarabine, cytarabine and granulocyte colony stimulating factor (FLAG regimen) to one of their treatment groups, and additionally idarubicine (FLAG-IDA regimen) to another group of 105 AML and MDS patients. The researchers were able to find no statistically significant difference between the two groups. They have achieved a CR of 59% during the study period of 4 years. They have recorded that EFS was 23% (range 11 months-5 years). In addition, Dluzniewska et al. (11) reported that the 3 year-OS for all disease groups was 61%; EFS, 54%; in the standard risk group OS was 81% and EFS was 70%; and in high risk group OS was 40% and EFS was 40%. The research investigated that the remission rate was 79% in whole group (98% in standard risk group and 63% in high risk group).

O'Brien et al. (12) administered daunomycine to one group of patients (group 1) and idarubicin to the other (group 2) in their research involving 268 patients with AML. They also administered idarubicin in two different dosages as 10 mg/m2 (group 2a) and 12 mg/m2 (group 2b). When they compare all three groups, there is no statistically significant difference in 5-year EFS and OS. In group 1, EFS was 50% and OS was 56%; in group 2a, EFS was 50% and OS was 60%; and in group 2b, EFS was 34% and OS was 50%.

Seo et al. (13) treated 125 newly diagnosed AML patients between 1983 and 1998. They began to administer more intensive therapy in 1990s than 1980s. They recorded that the CR rate was 58% for all patients. Six-year OS and DFS rates were 22% and 28% for patients with CR.

They noticed that the CR and OS rates were better and statistically significant in 1990s when compared to those of 1980s [CR was 69% and 54%, respectively (p=0.0016); OS was 32% and 15%, respectively (p=0.0014)]. Early deaths occured in the first 30 days and they were 9% in 1990 and 26% in 1980. Considering these findings, they reported that the difference was statistically significant. However, they were not able to report any significant improvement in DFS rates. Creutzig et al. (14) published the results of their multicentric study including 471 children received AML BFM 93 treatment protocol. Of these 471 patients, 161 were in standard risk group and 310 were in high risk group. They used daunorubicin or idarubicin together with cytarabine plus etoposide. They achieved remission in 87% of the patients. Five-year survival was 60%, EFS was 51%, and DFS was 62% in this patient population In the examination of bone marrow on the 15th day, blast>5% was observed in 17% of the patients of idarubicin group, while it was observed in 31% of daunorubicin group (p=0.007). When they compared AML BFM 93 to 87 protocols, they found that 5-year remission rates were 78% versus 68% and EFS rates were 44% versus 31% (p=0.01). They did not find any significant difference between the 5-year EFS and DFS rates of daunorubicin and idarubicin groups. In a current study OS and DFS rates were statistically significant (Breslow, Tarone-Ware), but EFS rates were not between two groups.

In conclusion, the survival of children with AML is still low; under 5 years, and we suggest that we can get better results by the protocol with idarubicin dose of 8 mg/m2/day. And we suggest that nutrition is important in patients with AML, if oral intake has impared particularly due to mucositis, TPN conduction can reduce mortality and morbidity. However, we suggest that preventive care should be conducted for the patients not to develop relapse.

REFERENCES

1. *Golub TR and Arceci RJ. Acute myelogenous leukemia. In Pizzo PA and Poplack DG: Principles and Practice of Pediatric Oncology. Lippincott Williams and Wilkins Company, Philadelphia, 4th edt. 2006; pp 591-644.*
2. *Sasmaz I, Tanyeli A, Bayram I, et al. The results of treatment with idarubicin in childhood acute nonlymphoblastic leukemia. Turk J Pediatr 2004; 46:32-7.*
3. *Heuvel-Elbrink MVA. Acute myeloid leukemia. In: Pinkerton R, Plowman PN, Pieters R. Paediatric oncology, third ed., Oxford University pres, 2004; 203-29.*
4. *Stahnke K, Boos J, Bender-Gotze C, Ritter J, Zimmermann M, Creutzig U. Duration of first remission predicts remission rates and long-term survival in children with relapsed acute myelogenous leukemia. Leukemia 1998;12:1534-8.*
5. *Thalhammer F, Geissler K, Jager U, et al. Duration of second complete remission in patients with acute myeloid leukemia treated with chemotherapy: a retrospective single-center study. Ann Hematol 1996;72:216-22.*
6. *Keating MJ, Smith TL, Kantarjian H, et al. Cytogenetic pattern in acute myelogenous leukemia: a major reproducible determinant of outcome. Leukemia 1988;2:403-12.*
7. *Webb DK. Management of relapsed acute myeloid leukaemia. Br J Haematol 1999;106:851-9.*
8. *Webb DK, Wheatley K, Harrison G, Stevens RF, Hann IM. Outcome for children with relapsed acute myeloid leukaemia following initial therapy in the Medical Research Council (MRC) AML 10 trial. MRC Childhood Leukaemia Working Party. Leukemia 1999;13:25-31.*
9. *Damon LE, Johnston LJ, Ries CA, et al. Treatment of acute leukemia with idarubicin, etoposide and cytarabine (IDEA). A randomized study of etoposide schedule. Cancer Chemother Pharmacol 2004;53(6):468-74.*
10. *Virchis A, Koh M, Rankin P, et al. Fludarabine, cytosine arabinoside, granulocyte-colony stimulating factor with or without idarubicin in the treatment of high risk acute leukaemia or myelodysplastic syndromes. Br J Haematol 2004; 124:26-32.*
11. *Dluzniewska A, Balwierz W, Balcerska A, et al. Efficacy of idarubicin in the treatment of childhood acute nonlymphoblastic leukemia: report of Polish Pediatric Leukemia/Lymphoma Study Group, Przegl Lek 2003; 60 Suppl 5:17-21.*
12. *O'Brien TA, Russell SJ, Vowels MR, et al. Australian and New Zealand Children's Cancer Study Group. Results of consecutive trials for children newly diagnosed with acute myeloid leukemia from the Australian and New Zealand Children's Cancer Study Group, Blood 2002; 100:2708-16.*
13. *Seo T, Fukushima T, Inoue H, et al. Long-term follow-up of the clinical efficacy of chemotherapy for acute myeloid leukemia at a single institute. J Infect Chemother 2001;7:156-62.*
14. *Creutzig U, Berthold F, Boos J, et al. AML-BFM-Studien-Gruppe. Improved treatment results in children with AML: Results of study AML-BFM 93. Klin Padiatr 2001;213:175-85.*