Research Article

The Effect of Using Prophylactic G-CSF during Chemotherapy on the Outcome of Children with Acute Lymphoblastic Leukemia

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Abstract

Background: Indications for the use of Granulocyte colony-stimulating factors (G-CSF) have so far been suggested to prevent febrile neutropenia, as well provide support for intensive chemotherapy. However, the long-term consequences of its use in children with acute lymphoblastic leukemia (ALL), especially in the time-sequenced setting, are not yet well understood. **Materials and Methods:** Children with newly diagnosed acute lymphoblastic leukemia ALL in Ali Asghar Children's Hospital were randomly assigned to two groups. Patients in both groups underwent chemotherapy according to the ALL IC-BFM 2002 protocol. Patients in Group A were supported in a time-sequenced setting during the second phase of induction and protocol mM and reinduction phase with G-CSF. However, patients in group B received G-CSF only during severe neutropenia or febrile neutropenia, as 5 μg/kg daily until there was an absolute neutrophil count (ANC) greater than 500/μl. **Results:** A total of 63 patients were included in the study. The total number of patients in both groups were as follows: 32 patients in group A (18 boys and 14 girls) and 31 patients in group B (11 boys and 20 girls). The number of high-risk patients in group A was higher, but this difference was not statistically significant. The recurrence rate in patients in group B was about seven times the recurrence rate in patients in group A, and the difference was statistically significant. In group A, no early relapse occurred, while nearly half of relapses in group B occurred as early relapses and the rest as late relapses. The 5-yr EFS rate was 96.90% ± 6.20% (95% CI) for patients in group A and 80.60 ± 14.20% (95% CI) for patients in group B, and this difference was statistically significant. **Conclusion:** In this study, prophylactic G-CSF prescribed in a time-sequenced setting not only does not increase the incidence of secondary leukemia in children with ALL but in addition to improving their prognosis, it reduces the recurrence rate in this group of patients. This finding needs to be confirmed by a larger study.

Keywords: Pediatric Acute Lymphoblastic Leukemia; Time-sequenced setting; Prophylactic G-CSF; Outcome

Abbreviations: BCP-ALL, B-cell precursor acute lymphoblastic leukemia; HR, high risk; IR, intermediate risk; IT, intrathecal; IV, intravenous push; max., maximum; PI, intravenous infusion; PO, by mouth; T-ALL, T-cell acute lymphoblastic leukemia; SR, standard

Introduction

The measure of Granulocyte colony-stimulating factors (G-CSF) is widely used to prevent febrile neutropenia in cancer patients undergoing chemotherapy. The American Society of Clinical Oncology (ASCO) and the European Organization for Research and Treatment of Cancer (EORTC) have provided appropriate guidelines for the indications for the use of G-CSF.[1,2] The effects of G-CSF have been proven in the following cases:

1. Reducing the risk of fever and neutropenia,
2. Reducing the length of stay in hospital,
3. Reducing the administration of injectable antibiotics, and increasing the tolerance of cytotoxic chemotherapy.[3-6]

Guidelines recommend the use of G-CSF when the chance of developing febrile neutropenia is greater than 20%.[7,8] However, there is still no evidence of the consequences of using G-CSF during the chemotherapy of children with cancer.

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The guidelines are based on the results of the treatment of adults with solid tumors and lymphoma who have been treated periodically and regularly with an almost constant treatment regimen [1,2]. But in the case of children with ALL, the chemotherapy protocol around the world follows an almost constant trend, including induction, consolidation, reinduction, and maintenance phases. The ALL IC-BFM 2002 chemotherapy regimen, one of the most authoritative treatment protocols for children with ALL, has been defined accordingly, and the high dose Methotrexate regimen has been added to the protocol instead of prophylactic cranial irradiation. Thus, different drug regimens are used during this treatment for children with ALL, and yield different effects on bone marrow suppression.

Preliminary studies on the use of prophylactic G-CSF have been performed to evaluate its effect on neutrophil recovery rate and speed, and there are very few studies in adults that have looked long-term consequences with the treatment in adults with all. [9-14].

In the present study, we investigated the effect of the preventive use of G-CSF prescribed in a time-sequenced setting during chemotherapy on the long-term outcome in children with all. [15,16]

Materials and Methods

During a case-control analytic study between 2007-2015, children with established B-precursor ALL between 1-16 years of age who were referred to the Ali Asghar Children's Hospital in Tehran (affiliated to the Iran University of Medical Sciences) entered the two groups after confirmation of diagnosis with bone marroe aspiration and flow cytometry. All patients were treated with the ALL IC-BFM 2002 chemotherapy regimen. In group A, patients routinely received G-CSF at the rate of 5 µg/kg/day during phase 2 of induction and the protocol mM and reinduction phase [Table 1].

Time schedule could be adjusted according to protocol guidelines if clinical condition/bone marrow recovery were inadequate. Corticosteroids were tapered over 9 days. In SR BCP-ALL, daunorubicin on days 22 and 29 was omitted. Doses were adjusted for children younger than 3 years. A loading dose of 10% was infused over 30 minutes, and the remaining 90%

Table 1: Treatment.

Treatment element/Drug	Treatment method	Protocol single dose	Per-day dose	Days of administration
	PO		60 mg/m^2	1-28[b]
Induction	**IV**	**1.5 mg/m^2 (max. 2 mg)**		**8, 15, 22, 29**
Protocol I' (SR BCP-ALL only) and protocol I (SR T-ALL, all IR and HR patients)	**PI over 1 hour**	**30 mg/m^2**		**8, 15, 22c, 29c**
Phase 1 Prednisone Vincristine Daunorubicin L-asparaginase	**PI over 1 hour**	**5,000 IU/m^2**		**12, 15, 18, 21, 24, 27, 30, 33**
	IT	**12 mg[d]**		**1, 12, 33**
Methotrexate Phase 2 Cyclophosphamide Cytarabine	**PI over 1 hour**	**1,000 mg/m^2**		**40, 75**
GCSF	**IV**	**75 mg/m^2**		**47-50, 54-57, 61-64, 68-71**
6-mercaptopurine	**SC**	**5 µg/kg**		**41-46, 51-53, 58-60, 65-67, 72-74, 76-81**
Methotrexate	**PO**		**60 mg/m^2**	**40-68**
	IT	**12 mg[d]**		**54, 68**
Consolidation				
Protocol mM (only BCP-ALL, SR/IR)				
6-mercaptopurine	PO		25 mg/m^2	
Methotrexatee	PI over 24 hour	2,000 mg/m^2		1-56
GCSF	SC	5 µg/kg		8, 22, 36, 50
Methotrexate	IT	12 mg[d]		15, 29, 43, 57
Protocol M (only T-ALL, SR/IR)				8, 22, 36, 50
6-mercaptopurine	PO		25 mg/m^2	
Methotrexatee	PI over 24 hours	5,000 mg/m^2		1-56 8, 22, 36, 50
Methotrexate	IT	12 mg[d]		8, 22, 36, 50
Delayed intensification	PO/IV	1.5 mg/m^2 (max. 2 mg)		
Protocol IIf	IV			
Phase 1	PI over 1 hour	30 mg/m^2		1-21b
Dexamethasone Vincristine Doxorubicin	PI over 1 hour	10,000 IU/m^2	10 mg/m^2	8, 15, 22, 29
L-asparaginase	PI over 1 hour	1,000 mg/m^2		8, 15, 22, 29
Phase 2 Cyclophosphamide Cytarabine	IV	75 mg/m^2		8, 11, 15, 18
6-thioguanine	PO		60 mg/m^2	36
Methotrexate	IT	12 mg[d]		43-46, 50-53
Interim maintenance therapy				36-49
Methotrexate	PO	20 mg/m^{2}g		43, 50
6-mercaptopurine	PO	50 mg/m^{2}g		
Maintenance therapyh				
Methotrexate	PO	20 mg/m^{2}g		
6-mercaptopurine	PO	50 mg/m^{2}g		

over 23.5 hours. Leucovorin rescue was given at hours 42, 48, and 54 (15 mg/m^2 each). Increased leucovorin doses were given if methotrexate levels at hour 42 or later were >1.0 µmol/L. If methotrexate level at hour 54 was >0.25 µmol/L, rescue was continued at 6 hour intervals until methotrexate levels were less than 0.25 µmol/L. Protocol II was given once in arms SR and IR as the only delayed intensification element, twice in arm HR with one 4-week interim maintenance therapy in between. Dose was adjusted according to WBC (target, 2,000 to 3,000/µL). Maintenance therapy started 2 weeks after the end of intensive therapy and was given until 104 weeks from diagnosis.

In goup A, GCSF was administered in these days, 5 µg/kg/s.c./daily: 41-46, 51-53, 58-60, 65-67, 72-74 and 76-81 during phase 2 of induction; 15, 29, 43 and 57 during consolidation; 9-14, 16-21, 23-28, 30-35, 37-42, 47-49 and 54-56.

Patients in group B received G-CSF only during severe neutropenia or febrile neutropenia as 5 µg/kg daily until the Absolute Neutrophil Count (ANC) was greater than 500/µl. In both groups, requirements for beginning of the second phase of induction were good general status, no severe infection, creatinine level within normal range for age, and recovering blood counts with the following parameters at least: WBC ≥ 2,000/µL, granulocytes ≥ 500/µL and platelets ≥ 50,000/µL. In addition, the minimum requirements to begin a cytarabine (ARA-C) block were: WBC ≥ 1500/µL and platelets ≥ 30,000/µL. As far as possible, a run ARA-C block should not be interrupted. However, should an ARA-C block be postponed or interrupted, then 6-Mercaptopurine (MP) also must be withheld for the same period of time. Also, blocks therapy (as mentioned in the IC-BFM 2002) was not used for high risk patients in both groups.

Then, the demographic data and the risk group defined according to the ALL IC-BFM 2002 protocol were extracted for each patient.

Data analysis

Patients' information was entered into SPSS v23.0. Descriptive data were analyzed by descriptive tests. The Kaplan-Meier test was used to determine Event-Free Survival (EFS). The Log-Rank method was employed to measure the survival rate and a P-value less than 0.05 was considered significant. Based on the median follow-up months (about 112 months), the estimated 10-years EFS values were determined for patients.

Ethical considerations

Patient information was only available to the executor and the name of the patient remained confidential. Research team members were aware of the details of Helsinki statement about ethic principles in medical research and were strictly committed to follow them in this research study. This project was approved at the Ethics Committee of the Iran University of Medical Sciences.

Results

There were a total of 63 patients included in the study. Thirty-two patients were in group A (18 boys and 14 girls) and 31 patients were in group B (11 boys and 20 girls). There were more boys in Group A, but the difference was not statistically significant (P=0.08 with Odds ratio=2.33 (0.84-6.44)). There was no statistically significant difference between the two groups in terms of mean age at diagnosis and initial WBC [Table 2].

The number of high-risk patients (according to IC-BFM2002 criteria for high-risk group) in group A was higher, but this difference was not statistically significant [Figure 1].

The number of patients over the age of 10 at the time of diagnosis was equal in both groups. The recurrence rate in patients in group B was about seven times the recurrence rate in patients in group A, and the difference was statistically significant [Figure 2].

In group A, no patients developed early relapse (recurrence in the first 18 months of diagnosis), while nearly half of relapses in group B were early relapse and the rest were late relapse (recurrence after 18 months of diagnosis). This difference was not statistically significant [Figure 3].

The highest recurrence rate was in bone marrow, which occurred in patients in group B [Table 3].

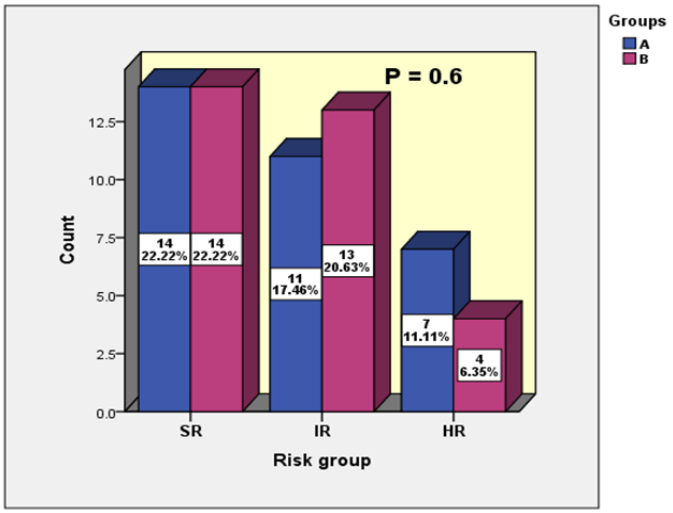

Figure 1: Comparison between two groups for distribution of patients with different risk groups.

Table 2: Means comparison between two groups.

	Groups	N	Mean	Std. Deviation	Std. error mean	P value
age at diagnosis (mo)	A	32	63.28	45.821	8.100	0.84
	B	31	65.47	41.355	7.428	
duration of follow-up (mo)	A	32	113.81	23.788	4.205	0.03
	B	31	97.45	34.304	6.161	
Initial WBC	A	32	11906.67	16885.189	3082.800	0.13
	B	31	21713.33	30742.902	5612.860	

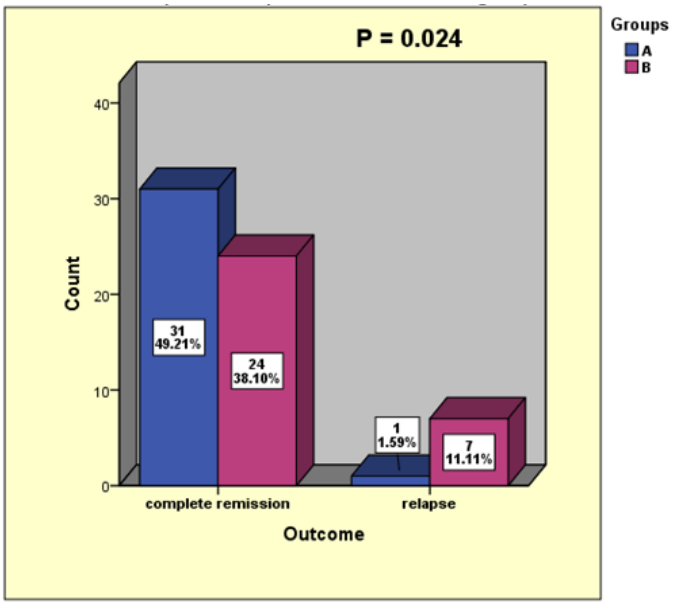

Figure 2: Comparison between two groups for outcome.

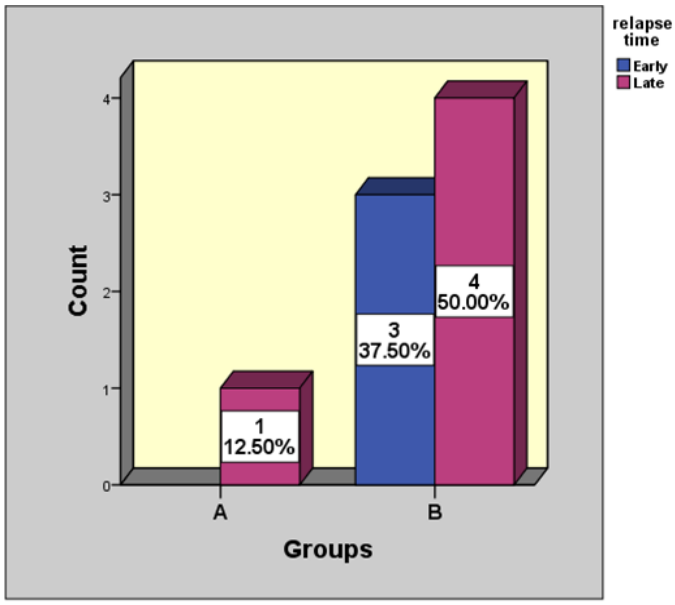

Figure 3: Comparison between two groups for relapse time.

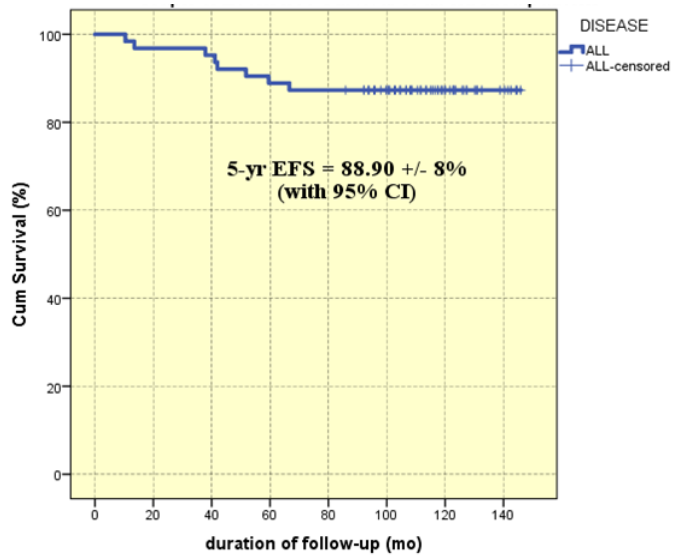

Figure 4: Event-free survival of all enrolled patients.

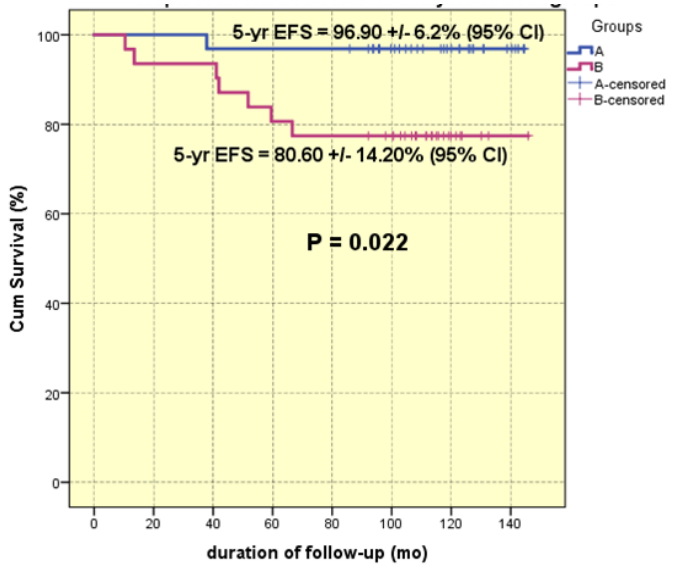

Figure 5: Event-free survival analysis of both groups.

The 5-yr EFS rate of all patients under study was 88.90 ± 8.00% (95% CI) [Figure 4].

Female patients had better EFS than male patients, with a 5-year EFS rate of 94.10 ± 8.00% (95% CI) for girls and 82.80 ± 14.00% for boys. However, this difference was not statistically significant. The 5-yr EFS rate was 96.90% ± 6.20% (95% CI) for patients in group A and 80.60 ± 14.20% (95% CI) for patients in group B, and this difference was statistically significant [Figure 5].

Discussion

Granulocyte colony-stimulating factors (G-CSF) can increase the number of neutrophils in healthy and sick people without complications. For many years, the use of G-CSF during chemotherapy has been discussed in patients with ALL, and there have been differences in research circles and groups around the world. [7,17] Initially, the drug was used to shorten the neutropenia caused by chemotherapy, especially in patients undergoing bone marrow transplantation. The American Society of Clinical Oncology provided a guideline for using G-CSF in 1994. G-CSF is used in cases of reducing febrile neutropenia in patients undergoing chemotherapy when the expectation is more than 40%, preventing the reduction of drug dose in the next cycle of chemotherapy, which is in cases where febrile neutropenia is proven, for the mobilization of peripheral blood progenitor cells from the bone marrow, and in the chemotherapy for solid tumors. However, its use was not recommended in patients with Acute Myeloid Leukemia (AML).[8] Through the use of a meta-analysis of randomized clinical trials, Wittman et al. examined the effect of prophylactic use of GCSF in reducing the incidence of febrile neutropenia in children undergoing chemotherapy. The authors observed a significant decrease in the frequency of febrile neutropenia, the duration of severe neutropenia and the patient's hospitalization, as well as the use of antibiotics. [17] On the other hand, Heath et al. conducted a study in 2003 in children with ALL. In their study, the children's cancer group, children with high-risk ALL [Patients were between 1 and 21 years old and untreated and had initial WBC counts> 50 × 10^9/L, hemoglobin 10 g/dL, or T-cell ALL and massive

lymphadenopathy (>3 cm), massive splenomegaly (below umbilicus), or a large mediastinal mass (more than a third of maximal transthoracic diameter)] were treated with the NY-1 or NY-2 protocol using Prophylactic G-CSF. They concluded that the only parameter that improved with Prophylactic G-CSF was the moderate time for severe neutropenia to resolve and in other cases, there was not much difference between the case and control groups.[18] In a study by the UICC EML REVIEW in 2014, it was found that when G-CSF was given to children during the first few days of initial induction or in the first course of chemotherapy (in post-remission), it increased secondary AML/Myelodysplastic leukemia (MDS) despite reducing neutropenia duration. [7]

The BFM chemotherapy regimen, one of the world's oldest and most reputable chemotherapy regimens for children with ALL, has dramatically increased survival rate over the past three decades. In a study of 5060 children with ALL treated with the ALL IC-BFM 2002 chemotherapy regimen, Stary and colleagues found that event-free survival and overall survival were 74% and 82%, respectively. However, these values were 81% and 90% for standard-risk patients, 75% and 83% for intermediate-risk patients, and 55% and 62% for high-risk patients, respectively. In this study, Prophylactic G-CSF was not used, and its use as prophylaxis is prohibited by almost all of the world's leading pediatric oncology treatment groups. [19] Other smaller studies have shown an improvement in the prognosis of children treated with the ALL IC-BFM 2002. [20,21] However, other studies have shown an improvement in the prognosis of this group of patients using Prophylactic G-CSF during chemotherapy., In a multi-centric randomized clinical trial, Holowiecki and colleagues (in 2002), examined the effect of G-CSF prescribed in time-sequenced setting during the induction and consolidation phase on 33 adults with ALL and observed a significant improvement in patients' prognosis. [22] In addition, the results of five randomized trials by EWALL published by Giebel et al. showed an improvement in leukemia-free survival following the use of Prophylactic G-CSF during the remission and induction phase for adults with ALL. [23]

There are other important findings of the study conducted, worthy of discussion, Shi, Guang Ye, et al. demonstrated that preventive use of G-CSF for febrile neutropenia improved prognosis in adults with all. [24] Our study was conducted in two groups, and prognosis of patients who received prophylactic G-CSF prescribed in time-sequenced setting during the phase 2 of induction and the protocol mM and reinduction phase with a group who received it only during severe neutropenia (ANC <500/ul) was compared. The significant increase in children's survival in the first group was very interesting, especially since the recurrence rate in the first group was much lower than in the control group. This finding is even more important when considering the duration of the study, and the hypothesis that the use of prophylactic G-CSF, especially prescribed in a time-sequenced setting, not only increases patient survival but also has no effect on increasing secondary leukemia/MDS. However, given the sample size of our study and other studies, a more comprehensive study with a larger sample size and a randomized multicenter study could help confirm this finding by adding to the body of evidence.

Conclusion

The use of G-CSF in treating children with ALL in the time-sequenced setting is not well understood. This study has helped to understand G-CSF therapy further by comparing two groups undergoing chemotherapy using different protocols. In this study, it was deduced that prophylactic G-CSF prescribed in a time-sequenced setting not only has no effect on increasing the incidence of secondary leukemia in children with ALL but in addition to improving their prognosis, it reduces the recurrence rate in this group of patients. Future researchers and clincians would be well-guided to build upon these findings and those of similar studies, through a study on a large scale. Ultimately it is hoped that these efforts may be lead to better treatment outcomes for pediatric patients with ALL.

Competing Interests

The authors indicate no potential conflicts of interest.

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