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Review Article

Overview the Causes of Early Deaths and Advance Supportive Care in Children with Acute Lymphoblastic Leukemia: A Systematic Review

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ABSTRACT

Introduction: The objective of this study is to determine the major causes of early death in acute lymphoblastic leukemia (ALL).
Methods: The following databases including PubMed, EMBASE, Science Direct and Google Scholar were searched for following terms: "acute lymphoblastic leukemia", "early mortality", "early death " and "death in induction phase ". Inclusion criteria were all studies about the etiologies of early mortality in children with acute lymphoblastic leukemia. Early death means death occurs within 30 days of starting induction chemotherapy.
Results: In total, 12 studies fulfilled inclusion criteria.7561 children under 18 years of age were studied in this review. Of these, 354 patients died during the induction phase of therapy. The early mortality rate was 4.6%±4.8. The most common cause of early death was an infection (52.5%), which was mainly bacterial. The second leading cause was bleeding (15%), and tumor lysis syndrome (4%) was the third most common cause. The other causes were septic shock (2%), hyperleukocytosis (2%), encephalopathy (1.7%), cardiomyopathy (1.7%), chemotherapy-related toxicity (1.2%), and thrombotic events (0.6%).
Conclusion: It is needed to advance supportive care to prevent infection by starting Intravenous immunoglobulin for infant and prophylaxis against Pneumocystis jiroveci with trimethoprim/sulfamethoxazole in neutropenic patients during induction, and bleeding by transfusion support.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer globally, and survival rates have improved over the past years in developed countries.[1, 2] The survival rates for children with ALL have considerably improved over the past decades. Current survival rates are approximately 80% for ALL. Although some patients with ALL have been cured, they may die due to causes other than persistent leukemia or relapse.[3]

The early death rate for ALL children has remained constant at about 5 %, despite the general improvement in overall survival.[4]

Some studies demonstrated that age at diagnosis was the only feature significantly associated with death during induction. Children 1–9 years old had a lower rate of death than infants or patients ≥10 years old during induction. In addition, there was a trend toward an increase in mortality rate during induction for patients with leukocyte count >100×10^9/L.[5]

The use of a stronger form of Escherichia coli asparaginase and the replacement of dexamethasone with prednisone contributed to a high rate of sepsis (6.5%) and death because of toxicity (11%) during induction therapy in two clinical trials.[6, 7]

The combined myelosuppressive effects of Daunomycin and dexamethasone may have associated with infection-related mortality during induction.[8] Patients who suffered from early death (ED) due to hemorrhage had presented

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more frequently with hyperleukocytosis. It also clarifies the higher frequency of ED in T-cell ALL patients, who present with higher initial white blood cells (WBCs). In addition, ED was often seen in Down syndrome patients.[3]

The most common causes of mortality during induction phase of treatment are infection, hemorrhage and drug related mortality.[3, 5, 8, 9]

The objective of this study is to identify the causes of mortality in children with ALL during induction phase of treatment and to find the strategies for decreasing early mortality.

Methods and Patients

The following databases including PubMed, EMBASE, Science Direct and Google Scholar were searched for relevant articles from September 1975 to September 2017. Following terms for searching review articles either alone or in combination were used: "acute lymphoblastic leukemia", "early mortality", "early death" and "death in induction phase". Then the relevant studies were filtered manually. All studies were assessed by authors from the aspect of quality assessment, and inclusion and exclusion criteria as summarized in the flow chart (Figure 1). Inclusion criteria included all studies about the etiologies of early mortality in children with acute lymphoblastic leukemia during the induction phase of treatment. Articles were excluded which had not explained the etiologies of early mortality. The articles were written in English, if not, the abstracts were in English.

All reported studies were analyzed with regards to the etiology of early death or mortality in the induction phase of ALL treatment, prognostic factors and the mortality rate. Early death or early mortality means death occurs before remission or within 30 days of starting induction chemotherapy.

Results

Twelve studies fulfilled inclusion criteria during the last 40 years (Figure 1). All studies were related to pediatric age group (age ≤18). The characteristic features of all studies are summarized in Table 1. Of 12 studies related to mortality of ALL in children, 7561 pediatric patients were evaluated. Of these, 354 ones died during the induction phase of treatment. The early mortality rate in this study was 4.7%. The etiologies of early mortality were infections, bleeding, tumor lysis syndrome, septic shock, encephalopathy, heart failure, thrombosis, syndrome of inappropriate antidiuretic hormone, uric acid nephropathy, hyperleukocytosis, and chemotherapy-related toxicity. The most common cause of early death was an infection (52.5%), which was mainly bacterial. The second leading cause was bleeding (15%), frequently reported brain hemorrhage, and tumor lysis syndrome (4%) was the third most common cause. The other causes of early mortality in order of frequency include septic shock (2%), hyperleukocytosis (2%), encephalopathy (1.7%), cardiomyopathy and heart failure (1.7%), chemotherapy-related toxicity (1.2%), thrombosis (0.6%), uric acid nephropathy (0.5%), and syndrome of inappropriate antidiuretic hormone secretion (0.25%).

The Characteristic features of patients and the etiologies of early mortality in this study were summarized in Table 1.

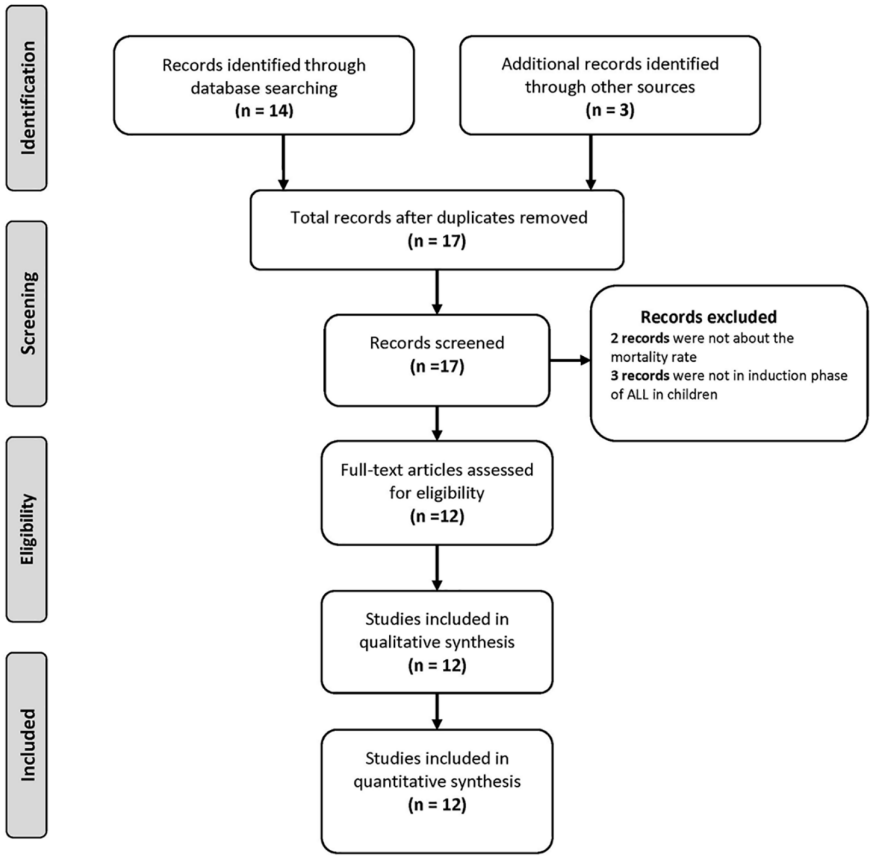

Figure 1: Flow chart study

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Table 1: Characteristics features of patients in review study

N	Author	Year	Number of patients	Number of early death (%)	Cause of early death	Reference
1	Slats AM	2005	875	9 (1%)	Bleeding (n=6) Infection (n=1) Unknown (n=2)	3
2	Martín-Trejo JA	2016	794	50 (6.3%)	Infection (n=26) Bleeding (n=7) Septic shock (n=7) Tumor lysis syndrome(n=6) Chemotherapy-related toxicity (n=4) Thrombosis (n=1)	10
3	Sumit Gupta	2011	1670	92 (5.5%)	Infection (n=47) Bleeding (n=17) Disease progression and other causes (n=28)	11
4	Salzer WL	2012	209	19 (9%)	Infection (=17) Bleeding (n=2)	12
5	Marwaha RK	2010	532	68 (12.8%)	Infection (n=35) Tumor lysis syndrome(n=8) Hyperleukocytosis(n=7) Bleeding (n=8)	13
6	Jaing TH	2009	1	1	Hyperammonemic encephalopathy due to asparginase(n=1)	14
7	Salzer W	2009	115	19 (16.5%)	Infection(n=19)	8
8	Dini G	1984	943	39 (4.1%)	Infection (n=20) Bleeding (n=11) Uric acid nephropathy (n=2) Cardiac failure (n=3) Unknown (n=3)	4
9	Hvizdala E	1984	379	12 (3.1%)	Infection (n=9) Bleeding (n=1) SIADH† (n=1) Unknown (n=1)	15
10	Bergmann K	2016	136	0	No mortality	16
11	Rubnitz JE	2004	1011	14 (1.4%)	Infection (n=11) Thrombosis (n=1) Encephalopathy (n=2)	5
12	Prucker C	2009	896	31 (3.4%)	Infection (n=21) Cardiomyopathy and heart failure (n=3) Encephalopathy (n=3) ICH‡ (n=1) Thrombosis (n=1)	17
			7561	354 (4.6%)		

†SIADH: Syndrome of Inappropriate Antidiuretic Hormone, ‡ICH: intracerebral hemorrhage

Discussion

In this article, we review the etiologies of early death in childhood acute lymphoblastic leukemia. As time goes by, improvement in antileukemia drugs has been achieved and survival of patients also has been increased but the mortality rate has remained constant during the induction phase of ALL in children. According to reported studies, the early mortality rate in childhood ALL is about 2-10%.[5, 17]

In this study, the cumulative early mortality rate is about 4.6%±4.8.

The differences of early mortality rate in different studies seem to be due to following causes: age of patients, sex, type of treatment, preexisting disorder like Down syndrome and high white blood cell count (WBC, defined as >100×10⁹/L).[3, 5]

In study of Slats AM and associates (2005), the prevalence of early death was higher in boys, t cell ALL, WBC>100×10⁹/L and Down syndrome.[3] In study of Rubnitz JE and associates (2004), among age, sex, leukocyte count, immunophenotyping and type of protocol, only age over 10 years at diagnosis was a prognostic factor of death unrelated to leukemia.[5]

Although prophylactic antibiotic decreases the mortality and morbidity rate of neutropenic fever in ALL mostly after induction therapy, induction and consolidation phases of treatment are associated with higher mortality rate due to infectious complication especially in infants.[8] The Daunomycin induced myelosuppressive and the lympholytic results of dexamethasone may have associated with infection related death during induction phase of treatment.[8] Replacing dexamethasone with prednisone during induction therapy for new case of ALL can cause a high incidence of infection related deaths. According to this complication, the replacement has no obvious advantage in the efficacy of remission induction

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for children with ALL.[6]

In this study, the most common cause of early mortality during induction phase was infection (52.5%). The other causes of early mortality in order of frequency include bleeding (15%), tumor lysis syndrome (4%), septic shock (2%), hyperleukocytosis (2%), encephalopathy (1.7%), cardiomyopathy and heart failure (1.7%), chemotherapy-related toxicity (1.2%), thrombosis (0.6%), uric acid nephropathy (0.5%) and SIADH (0.25%).

Study of Slats AM, showed that the most common cause of early death was bleeding,[3] whereas some studies showed that about 80% of all deaths during therapy had infectious causes and second cause of early death was bleeding.[5, 18-21]

The Children's Oncology Group P9407 replaced dexamethasone with prednisone during induction phase. Initial data from this study show a decline in infection related–mortality rate. Dexamethasone has greater central nervous system (CNS) penetration than prednisone therefore, it prevents CNS relapse more than prednisone.[8, 22]

Most of induction death occurs on or after 12 days of induction and the early death peaks are in third week.[11, 23]

According to data from this review study, it is necessary to advance our supportive care during induction therapy of ALL, including starting prophylaxis against Pneumocystis jiroveci with trimethoprim/sulfamethoxazole in neutropenic patients, intravenous immunoglobulin (IVIG) treatment for infant ALL during induction because of low immunoglobulin level in infant, influenza vaccination with the trivalent inactivated influenza vaccine in children with ALL and age above 6 months, transfusion support especially in critically ill patients, awareness of simultaneous use of azole compounds as antifungal agents with vincristine because of increased toxicity, performing early bronchoalveolar lavage in case of lower respiratory tract infection for detection of organism, prevention of tumor lysis syndrome with allopurinol, alkalinization and hyperhydration especially in high WBC count, and early diagnosis of fungal disease by detection of galactomannan test.[3, 8, 17, 24, 25]

Other strategies for reducing mortality among children with ALL include anthracyclines dose modifications during induction therapy that need further studies on induction protocol. Another strategy is to individualize the patients for using the type of corticosteroid during induction phase.[5, 12]

It is better to use dexamethasone due to highly CNS penetration in infant. Also, it is preferable to use prednisone instead of dexamethasone in patients older than 2 years without risk factor for CNS involvement due to lower risk of infection related mortality with prednisone.

Conclusion

We should advance our supportive care mainly to prevent infection and bleeding as well as anthracyclines dose modifications with performing further studies in order to reduce early mortality rate during induction phase of ALL.

Key points

- We should individualize the patients for using the type of corticosteroid during induction phase. It is better to use dexamethasone due to highly CNS penetration in infant. Also, it is preferable to use prednisone instead of dexamethasone in patients older than 2 years without risk factor for CNS involvement due to lower risk of infection related mortality with prednisone.
- It is better to start prophylaxis against Pneumocystis jiroveci with trimethoprim/sulfamethoxazole in neutropenic patients who are not glucose-6-phosphate dehydrogenase deficient.
- It is better to use intravenous immunoglobulin (IVIG) for treatment of infant ALL during induction because of low immunoglobulin level in infant, influenza vaccination with the trivalent inactivated influenza vaccine in children with ALL and age above 6 months, transfusion support especially in critically ill patients

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