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Impact of supportive care on ALL Induction Mortality; the Better, the Less

KEYWORDS

induction mortality, Acute Lymphoblastic leukemia, Induction deaths, ALL induction mortality

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ABSTRACT Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy with excellent treatment outcomes. Treatment related mortality is highest during induction phase of treatment with infection being the major cause of mortality. Though the mortality has significantly decreased in patients treated under clinical trial setting and in developed countries, mortality is still high in developing countries. Both treatment and hospital related factors contribute to induction mortality. A retrospective analysis of induction deaths and its causes in patients less than 21 years from January 2011 to June 2016 is performed. Two patients (0.9%) died during induction phase. An induction mortality of less than 1% in our institution can be considered as national benchmark. Availability of supportive care services and promptness in administration of antibiotics and platelets play a pivotal role in bringing down the induction deaths.

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood with excellent treatment outcome. Treatment of ALL includes induction, consolidation and maintenance phases. Induction phase of treatment is the most important phase of therapy as further treatment plan depends on response to induction therapy. As the induction phase of therapy involves treatment of the patient with compromised bone marrow, complications are also high during this phase sometimes leading to death of the patient. Induction mortality accounts for about one-tenth of all ALL-associated deaths and up to 50% of all treatment-related mortality.[1,2]

Though the data on induction mortality from cooperative group chemotherapy trials have come down from 2.16% (1990–1994) to 1.57% (2000–2005),1 mortality is still high in patients treated outside clinical trial setting.

Good supportive care is the backbone of induction therapy of ALL and the advent of newer generation antibiotics and antifungals have gone a long way in reducing induction mortality in ALL. Apart from the availability of drugs, promptness in administering supportive care is also important.

Patients and Methods

A retrospective analysis of all the patients less than 21years old who received induction chemotherapy for Acute Lymphoblastic Leukemia from January 2011 to June 2016 is performed. Both T and B cell subtypes are included. We studied the number of deaths and causes of mortality in those patients.

Results

Below the age of 21 years, a total of 221 patients received induction therapy for ALL during the study period. The protocol followed was MCP 841 for 190 patients and BFM 95 for 31 patients. Antibiotic prophylaxis was given for all the patients with cefixime or levofloxacin, fluconazole and trimethoprim-sulfomethoxazole during the induction period.

Table 1: Induction protocol for ALL, MCP841

Drugs	Dosage	Days		
Inj Daunorubicin	30mg/sqm	8,15,29		
Inj Vincristine	1.5mg/sqm	1,8,15,22,29		
Inj L-Asparginase	6000IU/sqm	10 doses		
Tab Prednisolone	40mg/sqm	1 to 29		
ITMtx	12mg	1,8,15,22		

Table 2: Induction protocol for ALL, BFM 95

Drugs	Dosage	Days
Inj Daunorubicin	30mg/sqm	8,15,22,29
Inj Vincristine	1.5mg/sqm	8,15,22,29
Inj L-Asparginase	5000IU/sqm	12,15,18,21,24,27,30,33
Tab Prednisolone	60mg/sqm	1 to 28
ITMtx	12mg	1,12,33

There are two patients with Downs syndrome in the study period and both of them survived. Dose modifications are done for Downs children.

Of the 221 patients, 2 patients (0.9%) died during induction. One ten year old boy died on the second day of admission with intracranial bleed. The second seven year old girl child died on day 9 of therapy with gastroenteritis leading to septicemia and renal failure. There was a delay in the start of antibiotics for this patient as the child's parents did not reveal about diarrhea until recognition by the physician with clinical signs by which time it was too late. Blood cultures grew E.coli.

Discussion

Induction mortality in developed countries is less than 3% even outside the clinical trial setting while it is high in developing countries.3-5 Infection is the major cause of treatment-related mortality in pediatric acute lymphoblastic leukemia and is greatest during the induction phase.6 Children with Down syndrome are at high risk for infection-related mortality

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throughout all treatment phases.[6]

In our study, antibiotic prophylaxis is given to all the patients throughout the induction phase and intravenous antibiotics are started at the first sign of infection and also to those presenting with sepsis. This might have played a role in reducing induction deaths.

In a study by Muhammad Asim7 et al from Pakistan, 52.7% died during induction therapy from 2001 to 2005, with infection as the major cause of mortality. Mubtsih et al8 and Mostert et al9 from Indonesia reported 29% and 23% mortality respectively in children due to complications while on treatment for ALL. In the study by Advani.S et al10 from India, 36 out of 530 patients (6.79%) died during induction phase, with infection being the major cause of mortality.

In a study from AIIMS, a total of 250 children up to 15 years age from June 1992 to June 2002 with newly diagnosed ALL were included and were uniformly treated on MCP 841 protocol. There were 27 induction deaths (10.8%).[11]

Other Indian studies by Bajel et al12 (2008), Kulkarni et al13 (2009), Arya et al14 (2010) and Radhakrishnan et al15 (2015), report induction mortality of 2%, 12.8%, 11.0% and 3.3% respectively.

An induction mortality of less than 1% in our institution can be considered as national benchmark. This can be attributed to multiple factors. First is the government factor with the introduction of insurance scheme for the poor. This has made free treatment available to a large number of deprived patients. This has also increased the number of patients undergoing treatment.

Second is the hospital administration factor which makes the drugs and blood components readily available. Inspite of insurance schemes all the hospitals are not geared with the same facilities in our country. It is the hospital policy that determines the prompt availability of medicines and blood products.

Third and the most important are the supportive care services like biochemistry, pathology and microbiology. Most of the hospitals in developing countries especially those in government sector and including those like Regional Cancer Centers, are lacking in good supportive care services. Lack of blood components in the hospital premises, lack of culture backup for decision on antibiotics are very common in most of the government hospitals. A 24 hour availability of the supporting staff in our institution has helped in bring down the treatment mortality considerably.

Conclusion

Supportive care is an essential component of induction therapy for ALL. Early identification of infection, prompt administration of antibiotics, strict vigilance on platelet count play a pivotal role in bringing down the mortality during induction therapy.

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