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Review Article

Induction-Related Mortality in Adults with Acute Lymphoblastic Leukemia (ALL) Treated in Two Consecutive Protocol Eras 1998-2006 and 2007-2016

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Summary

Induction mortality is the price adult acute lymphoblastic leukaemia pays for the intensity that cures it. Successive protocol generations raised dose intensity to improve remission depth, and in older adults the toxicity outran the benefit. The most instructive recent evidence comes from cooperative groups that compared consecutive protocol eras directly and found that reducing intensity in middle-aged patients lowered early death without loss of disease control.

Objectives: To review the published evidence on induction-related mortality in adults with acute lymphoblastic leukaemia across consecutive protocol generations: how rates have changed, which patients carry the risk, what they die of, and what protocol modifications have demonstrably reduced it.

Material and Methods: Narrative review of cooperative group trials, population-based registry analyses and single-centre cohorts indexed in PubMed and the major haematology journals. Studies were eligible if they reported induction or treatment-related mortality in a defined leukaemia population, or compared outcomes between consecutive treatment protocols. No new patient data were generated and no patients were recruited; every rate and effect estimate quoted is one published by the original investigators.

Results: In a direct comparison of two consecutive cooperative group protocols enrolling 787 and 743 adults respectively, the induction death rate fell from 6 to 3 per cent ($p = 0.005$). The reduction was confined to patients aged 45 to 59 years, in whom it fell from 11 to 3 per cent ($p = 0.001$) after de-escalation of asparaginase, anthracycline and corticosteroid dosing, at the cost of a higher requirement for a second induction course (9 against 5 per cent). Excess intensity is demonstrably harmful in this age group: in a prospective trial giving pegylated asparaginase within a five-drug induction to 90 adults of median age 46.5, sixteen died during induction, and age above 40 years carried an odds ratio for induction death of 18.5 (95% CI 2.02-169.0). Reported induction mortality ranges from 7 to 11 per cent in high-resource trial settings to 20 to 50 per cent in some Latin American series, with 13.4 per cent in one Hispanic adult cohort. Infection accounts for the majority of deaths, at 68 per cent in a population-based analysis and 64.1 per cent in a Hispanic cohort.

Conclusion: The fall in induction mortality between protocol generations is attributable to age-adapted de-escalation rather than to better supportive care alone, and the benefit is concentrated in middle-aged adults. Reporting induction mortality as a single figure for an adult trial conceals an age gradient steep enough to determine whether a protocol is safe.

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, AYA – Adolescent and Young Adult, BFM – Berlin-Frankfurt-Münster, CR – Complete Remission, HSCT – Haematopoietic Stem Cell Transplantation, IRM – Induction-Related Mortality, MRD – Minimal Residual Disease, Ph – Philadelphia Chromosome, TRM – Treatment-Related Mortality, TKI – Tyrosine Kinase Inhibitor, WBC – White Blood Cell Count.

Keywords: *Acute Lymphoblastic Leukaemia; Induction Mortality; Treatment-Related Mortality; Age-Adapted Chemotherapy; Protocol Era*

Introduction

Acute lymphoblastic leukaemia accounts for roughly a fifth to a third of acute leukaemia in adults, and its treatment differs from the paediatric disease less in the drugs used than in how well they are tolerated [1,2]. Adult protocols have converged on paediatric-inspired backbones because they produce deeper remissions, but the same intensity that benefits a twenty-year-old is frequently lethal at fifty [3,4]. The paediatric-inspired approach itself is well founded: applied to 295 adults aged 17 to 39, it gave treatment-related mortality of 3 per cent and

three-year overall survival of 73 per cent against 55 per cent in earlier studies of the same age group [18], and the European experience with pediatric-inspired therapy in Philadelphia-negative disease pointed the same way [19]. Earlier dose-intensive adult regimens [21] and large international trials [20] established the benchmark those protocols improved on.

Induction-related mortality is therefore not a fixed property of the disease but of the protocol applied to it. Successive cooperative group generations have adjusted dose intensity, asparaginase scheduling and transplant indication, and several groups have compared consecutive eras directly [5,6]. Those comparisons are the most informative evidence available, because they hold the population roughly constant while the protocol changes.

The paediatric experience establishes what is achievable. Population-based analysis of five consecutive Berlin-Frankfurt-Münster trials showed the ten-year cumulative incidence of treatment-related death falling from 6 per cent to 2 per cent across protocol generations, with induction death specifically falling from 2.2 per cent to 0.2 per cent [7]. British trials over a comparable period reported the same direction of travel [8], as did single-institution series [9].

Adults have not matched that trajectory, and this review sets out what the published comparisons between consecutive protocol eras show, which patients carry the residual risk, and what they die of.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and oncology journals were searched for studies of early mortality in acute lymphoblastic leukaemia. Search terms combined acute lymphoblastic leukaemia with induction death, induction-related mortality, treatment-related mortality, protocol era, asparaginase toxicity and age-adapted chemotherapy. Reference lists of retrieved trials and registry analyses were screened by hand.

Eligibility: Studies were included if they reported induction or treatment-related mortality in a defined population with acute lymphoblastic leukaemia, or compared outcomes between consecutive protocols within the same cooperative group. Paediatric and adolescent series are included where they establish the achievable benchmark or the age gradient, and are identified as such.

Data extraction and handling: Design, cohort size, protocol, age distribution and reported mortality with associated p values were extracted as published. Age band is reported alongside every mortality figure, because the gradient across adult age is steeper than the difference between most protocols. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 3 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What changed between consecutive protocol eras: The clearest evidence comes from a cooperative group that compared 743 patients treated on a later protocol against 787 treated on its immediate predecessor, in populations that did not differ significantly in age, sex, lineage or white cell count. Two changes were introduced: chemotherapy intensity was reduced in patients aged 45 to 59, and the transplant indication was narrowed to rest on minimal residual disease response rather than baseline risk features [5,6].

The induction death rate fell from 6 to 3 per cent ($p = 0.005$). Crucially, the reduction was confined to the age group in which intensity had been de-escalated, falling from 11 to 3 per cent in patients aged 45 to 59 ($p = 0.001$) (Figure 1) [5]. The trade-off was a higher requirement for a second induction course, 9 against 5 per cent, without a corresponding loss of overall survival [5,6]. De-escalation of asparaginase, anthracycline and steroid dosing in patients aged 45 or more produced a more than threefold reduction in early death [6].

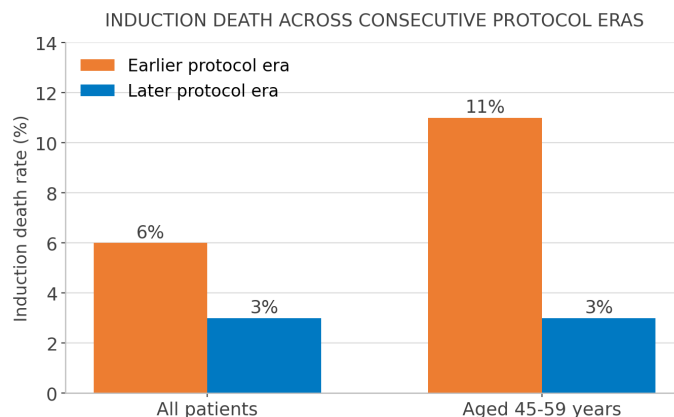


Figure 1: Induction death rate across two consecutive cooperative group protocols, overall and in middle-aged adults [5]

Excess intensity is demonstrably harmful: The case for de-escalation does not rest on inference. A prospective trial gave pegylated asparaginase on days 4 and 18 within a five-drug induction to 90 adults aged 25 to 65, median age 46.5. Sixteen died of treatment-related causes during induction, and the median age of those who died was 56; eight of the sixteen died of sepsis combined with hepatotoxicity [10].

Age was the dominant predictor. Patients over 40 carried an odds ratio for induction death of 18.5 (95% CI 2.02-169.0, $p = 0.01$) against those aged 40 or under, and Philadelphia-negative disease an odds ratio of 13.60 (95% CI 3.52-52.36, $p < 0.001$). Among the 74 survivors, half had at least one grade 3 or 4 asparaginase-related adverse event, most often hepatotoxicity in 27 patients (36.5 per

cent) [10]. The protocol was amended to omit the day 4 infusion above 40 years and reduce anthracycline exposure [6,17].

Other groups reached the same conclusion independently. Asparaginase dosing was made age-adapted with reduced doses above 55 years in one national protocol [6,11], and asparaginase is now widely regarded as too toxic at paediatric doses in older adults despite its contribution to outcome in younger patients [1]. The pattern across groups is consistent: the drug that most improves remission depth in adolescents is the one that most reliably kills middle-aged adults. In Philadelphia-positive disease the calculus differs again, since targeted therapy with corticosteroids alone induces remission in elderly patients without cytotoxic chemotherapy [25].

Where the patient is treated matters as much as the protocol: Reported induction mortality varies more between healthcare settings than between protocol generations. Rates of 7 to 11 per cent are reported from high-resource trial settings, against 20 to 50 per cent in some Latin American series, with 13.4 per cent in a Hispanic adult cohort of 170 patients treated between 2009 and 2016 (Figure 2) [12,13].

A separate cohort of 167 adolescents and adults treated in a low- and middle-income setting over the same period examined whether the excess reflected disease biology or treatment-related complications, and attributed it principally to the latter [13]. That distinction matters because it identifies the excess as addressable by supportive care and dose adaptation rather than as an intrinsic feature of the population.

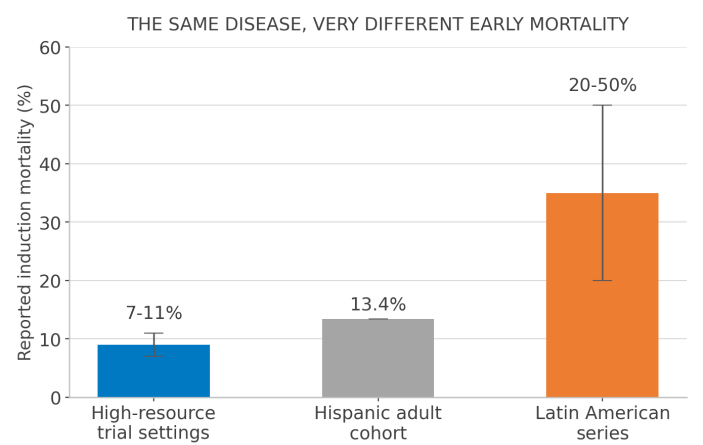


Figure 2: Reported induction mortality by treatment setting [12,13]

Study	n	Population	Principal reported finding
Hargrave et al. 2001 [8]	—	Children	Progressive fall in treatment-related death, 1980-1997
Rubnitz et al. 2004 [9]	—	Children	Death during induction and first remission characterised
Mann et al. 2009 [7]	896	Children	Induction death fell from 2.2% to 0.2% across eras
Pichler et al. 2013 [4]	—	Adolescents	Inferior outcome driven by toxicity, not relapse
Patel et al. 2017 [10]	90	Adults	16 induction deaths; odds ratio 18.5 above age 40
Dombret et al. 2022 [5]	1,530	Adults	Induction death 6% to 3% across consecutive protocols

Table 1: Principal studies reviewed, with population and the finding as reported by the original investigators

What patients die of: The cause of death is remarkably consistent across settings. In a population-based analysis of 896 children, 21 of 31 deaths (68 per cent) were from infectious complications and 10 (32 per cent) from non-infectious causes (Figure 3) [7]. In the Hispanic adult cohort, 64.1 per cent of induction deaths were infection-related, with pneumonia the commonest source at 39.8 per cent; Gram-negative organisms were more prevalent, but mortality was higher when the organism was Gram-positive, at 26.3 against 13.6 per cent (p = 0.028) [12].

In a paediatric-inspired regimen applied to Philadelphia-negative adolescents and young adults, induction-related mortality was 4.2 per cent, split evenly between septicaemia and haemorrhagic complications, and multivariate analysis identified treatment with an adult rather than paediatric-inspired regimen as a significant risk factor for infectious complications [14].

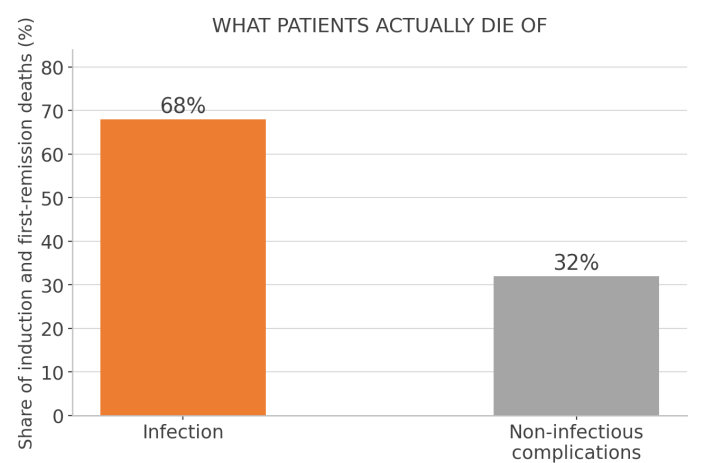


Figure 3: Cause of induction and first-remission death in a population-based paediatric analysis [7]

Factor	Direction of effect	Evidence
Age above 45 years	Substantially raises risk	11% against 3% induction death on intensive dosing [5]
Intensive asparaginase	Raises risk	16 of 90 died in induction; 36.5% hepatotoxicity [10]
Age-adapted de-escalation	Lowers risk	More than threefold reduction in early death [6]
Adult rather than paediatric regimen	Raises infectious risk	Independent predictor on multivariate analysis [14]
Resource-limited setting	Raises risk	20-50% against 7-11% in trial settings [12,13]

Table 2: Factors reported to raise or lower induction-related mortality in adults

Discussion

The improvement between protocol generations is real, and its cause is specific. Induction death halved between two consecutive cooperative group protocols, and the entire reduction occurred in the age band where intensity had been deliberately lowered [5,6]. That is a stronger inference than the usual explanation of improving supportive care over time, because supportive care improved for all age groups while the mortality reduction did not.

The corollary is that the earlier protocol was overtreating middle-aged adults. An 11 per cent induction death rate in patients aged 45 to 59 [5], and sixteen deaths among 90 patients in a trial using intensive asparaginase [10], describe regimens whose toxicity had overtaken their benefit. Those rates were reported at the time and interpreted as the cost of cure; the de-escalation data show they were avoidable.

Why a single mortality figure is misleading

Reporting induction mortality for an adult trial as one number conceals a gradient steep enough to change whether a protocol should be used. In the same trial, the rate was 3 per cent overall and 11 per cent in patients aged 45 to 59 [5]. A group publishing only the aggregate would appear to have a safe protocol while a third of its population was being treated unsafely.

The same argument applies across settings. A protocol validated at 7 to 11 per cent induction mortality in high-resource trial centres may run at several times that where supportive care is thinner [12,13], and the excess has been attributed to treatment-related complications rather than disease biology [13], which makes it a modifiable feature of implementation rather than an argument against the protocol.

Study limitations

The limitations belong to the underlying literature. Comparisons between consecutive protocol eras are not randomised, so

improvements in supportive care, antimicrobial practice and patient selection over time cannot be fully separated from the protocol change [5,6]. Several informative analyses are of paediatric or adolescent populations and transfer imperfectly to adults [4,7,8,9,15]. The upper age boundary of the adolescent and young adult approach is itself contested [22], and the component drug schedules were derived from paediatric trials [23] with adult adaptations examined only retrospectively [24]. Definitions of induction death differ between groups in both the time window and whether deaths in resistant disease are counted [12,13]. Single-centre and resource-stratified cohorts are small and their case mix differs substantially [12,13,14]. And trial populations are selected for fitness, so reported mortality understates what occurs in unselected practice [1,2]. Older adults in particular are under-represented, and dedicated guidance for that group has had to be developed separately [16].

Two gaps deserve naming. No randomised comparison has tested age-adapted against standard dosing with induction mortality as the primary endpoint, so the de-escalation evidence remains a between-protocol comparison [5,6]. And no study reviewed here reports whether the higher rate of second induction courses after de-escalation carries a downstream cost in relapse or transplant eligibility [5].

Conclusion

Induction mortality in adult acute lymphoblastic leukaemia fell from 6 to 3 per cent between two consecutive cooperative group protocols, and the reduction was entirely attributable to lowering chemotherapy intensity in patients aged 45 to 59, in whom it fell from 11 to 3 per cent. Intensive asparaginase in adults of median age 46.5 killed sixteen of 90 patients during induction, with an odds ratio of 18.5 for death above age 40, which is toxicity without compensating benefit. Infection causes roughly two thirds of these deaths across every setting examined, and reported rates range from 7 to 11 per cent in trial centres to 20 to 50 per cent elsewhere. Age-adapted dosing is the intervention with demonstrated effect, and reporting induction mortality by age band rather than as a single trial figure is what would make the next comparison interpretable.

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Credit for the material assembled here belongs to the cooperative study groups whose consecutive protocol cohorts it draws on.

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Conflict of Interest

Not one of the authors declares a competing interest.

Ethics Statement

Only studies already in the published record are examined here. Nobody was recruited and no new patient data were gathered, so the work needed no ethical approval.

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