Lack of clarity in the definition of treatment-related mortality: pediatric acute leukemia and adult acute promyelocytic leukemia as examples

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Treatment-related mortality (TRM) is important in acute lymphoblastic leukemia and acute myeloid leukemia (AML); however, little is known about how TRM is defined across trials. Two major problems are related to what constitutes treatment versus disease-related cause of death and to TRM attribution (for example, death because of infection or hemorrhage). To address the former, we conducted a systematic review of randomized therapeutic pediatric acute leukemia and adult/pediatric acute promyelocytic leukemia trials and any study type focused on TRM in pediatric acute leukemia. We described definitions used for TRM. Sixty-six studies were included. Few therapeutic pediatric acute lymphoblastic leukemia studies (2/32, 6.3%) provided definitions for TRM, whereas more therapeutic pediatric AML studies (6/9, 66.7%) provided definitions. There was great heterogeneity in TRM classification. The authors of most studies relied on deaths during induction or in remission to delineate whether a death was TRM. However, 44.4% of therapeutic AML studies used death within a specific time frame to delineate TRM. We suggest that a consistent approach to defining and determining attribution for TRM in acute leukemia is an important future goal. Harmonization of definitions across the age spectrum would allow comparisons between pediatric and adult studies. (*Blood*. 2011;118(19): 5080-5083)

Introduction

Outcomes for children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) have significantly improved over time, with overall survival rates currently ranging from 83% to 94% for ALL[1] and 60% to 65% for AML.[2] Improvement in survival for adults with acute leukemia, particularly in acute promyelocytic leukemia (APL), has also been demonstrated.[3] This success has been the result of multiple factors, including improved risk stratification, intensification of therapy for those with poorer prognosis, incorporation of all-*trans* retinoic acid in APL, and improvements in supportive care. However, further improvement in outcomes likely will arise through targeted therapies and through lowering the proportion of deaths attributed to treatment.

A better understanding of treatment-related mortality (TRM) is important. TRM is an important contributor to poor outcomes for both children and adults with ALL and AML, particularly in the high-risk and relapse settings. An understanding of the proportion of events that occur because of relapse/progressive disease versus TRM is critical for several reasons. First, this understanding may suggest situations in which intensification of therapy may be a more or less effective strategy overall. For example, if events are primarily because of TRM, then therapy should be modified to become less intensive. Second, this information will allow for a better understanding of when more careful monitoring is required and where supportive care strategies should be directed. However, from our experience, we have found that definitions for TRM are not clear and that authors may define TRM differently, even in different reports arising from the same study.[4,5] Consistency in defining TRM is critically important. If studies define TRM differently, then variable rates of TRM may be because of heterogeneous definitions rather than the toxicity of therapy, and thus, this confusion may derail plans to optimize therapy. This article will address inconsistency in defining TRM and issues related to attribution of cause of death.

Inconsistency in defining TRM

Cause of death is important information used for clinical, administrative, and research purposes. In all 3 areas, inconsistency in defining a death as related to treatment or disease is so prevalent that this information may be of little use in some settings. Areas that may be controversial when determining whether a death is related to treatment in acute leukemia include death before initiation of chemotherapy; deaths because of suicide, accidents, and unknown causes; those that occur after completion of therapy; and those that occur after HSCT. In the last example, in some reports, patients with ALL are censored when they begin HSCT, whereas in other reports, deaths that occur after HSCT (both short and long-term) in patients who remain in remission following the procedure are included as TRM. In another setting, for both ALL and AML, early deaths after starting treatment because of hyperleukocytosis may be differentially classified as TRM or disease-related death. Furthermore, TRM classification may be determined by death during induction therapy or while the patient is in remission, or alternatively on the basis of some time frame from diagnosis or treatment initiation.

Using these considerations, we conducted a systematic review of leukemia trials to describe how TRM has been defined. We

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Table 1. Summaries of TRM reporting in acute lymphoblastic leukemia, acute myeloid leukemia, and acute promyelocytic leukemia trials

	Provide definition of TRM	Describe TRM over entire course of treatment	Include deaths before starting chemotherapy*	Include deaths after completing chemotherapy	Include deaths after stem cell transplantation	Include accidents, suicide, or unknown	Use time from start treatment to define TRM
Pediatric acute lymphoblastic leukemia N = 32	2 (6.3)	2 (6.3)	2 yes; 12 no; 2 exclude; 12 unknown; 4 NA	6 (18.8)	6 (18.8)	6 (18.8)	1 (3.1)
Pediatric acute myeloid leukemia N = 9	6 (66.7)	3 (33.3)	4 yes; 2 no; 2 unknown; 1 NA	1 (11.1)	5 (55.6)	2 (22.2)	4 (44.4)
Studies of TRM in pediatric acute leukemia N = 10	7 (70.0)	8 (80.0)	4 yes; 2 no; 4 unknown	3 (30.0)	7 (70.0)	5 (50.0)	3 (30.0)
Adult and pediatric acute promyelocytic leukemia N = 15	8 (53.3)	0 (0)	1 yes; 3 no; 5 exclude; 6 unknown	1 (6.7)	0 (0)	4 (26.7)	4 (26.7)

Values are n (%).

NA indicates not applicable; and TRM, treatment-related mortality.

*Yes indicates that the study classified deaths before starting chemotherapy as early death or TRM; no, no deaths before starting treatment; exclude, specifically excluded deaths before starting treatment in the outcome analysis; unknown, we could not ascertain how deaths before starting treatment were handled; and NA, study did not include patients in induction.

performed electronic searches of Ovid MEDLINE and EMBASE from 1980 to May 2011 and evidence-based medicine reviews from 1980 to the second quarter of 2011. We focused on 3 types of acute leukemia trials, namely (1) pediatric (age defined by each study but generally included patients up to 18 or 21 years of age) randomized therapeutic trials in ALL and AML; (2) any type of study in which TRM was a main outcome in pediatric ALL and AML patients; and (3) adult and pediatric randomized therapeutic trials in APL. We limited our analysis to publications from 1990 and forward to ensure that we captured definitions used in more recent trials (our strategy is provided in supplemental Figure 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Inclusion and exclusion criteria were defined a priori. Therapeutic studies were included if (1) the population consisted of newly diagnosed ALL, AML, or APL (ie, not relapsed); (2) there was randomization of an antileukemic treatment in any arm of the study (to ensure that the study was conducted prospectively); (3) pediatric subjects were included for the ALL and AML (non-APL) search and all ages for the APL search; and (4) treatment did not solely consist of HSCT. Exclusion criteria were as follows: (1) no randomized intervention; (2) randomized intervention not related to leukemia therapy; (3) study population consisted of adults or pediatric data not abstractable only for the ALL and AML (non-APL) search; (4) population solely infant ALL or mature B-cell ALL; and (5) duplicate publication. When duplicate publications were identified, the publication with the longest follow-up was chosen. Reviews in which the authors summarized multiple studies were excluded because detailed methods typically were not presented. For studies in which TRM was a main outcome, study eligibility was similar but restricted to children. Studies were included if (1) the population consisted of newly diagnosed ALL or AML (non-APL); (2) TRM was primary or secondary outcome; (3) they included pediatric subjects; and (4) treatment did not solely consist of HSCT. We restricted studies to those that were published in manuscript format (which excluded conference proceedings only) and to those published in the English language.

One reviewer (M.-C.E., E.B., or L.S.) evaluated the titles and abstracts of publications identified by the search strategy, and any potentially relevant publication was retrieved in full. Final inclusion of studies into the systematic review was by agreement of 2 reviewers. The reviewers were not blinded to study authors or outcomes. Data abstraction was performed by 2 reviewers (M.-C.E. and L.S.) with the use of a standardized data collection form.

Supplemental Figure 2 illustrates the flow diagram of trial identification and selection. A total of 3828 titles and abstracts were reviewed; 151 articles were retrieved for detailed evaluation, and 66 satisfied eligibility criteria: 32 were therapeutic pediatric ALL studies, 9 were therapeutic pediatric AML studies, 10 were studies of TRM in pediatric ALL or AML, and 15 were therapeutic adult or pediatric APL studies. Reasons for exclusion are listed in supplemental Figure 2. Demographics of the 66 included studies are presented in supplemental Tables 1 through 4, which provides more detailed comments about description of TRM. Table 1 summarizes the information pertinent to TRM definitions for the 4 groups of studies. The definition of TRM was rarely included in therapeutic pediatric ALL studies (6.3%) but was more common in pediatric AML and TRM studies (66.7% and 70.0%). The definition of TRM was intermediate for APL (53.3%), but all of these definitions were for early death rather than TRM specifically (supplemental Table 4).

Very few therapeutic trials presented the TRM rate across the trajectory of treatment; in other words, they only presented TRM by phase of therapy such as during induction or in remission. Among the 4 groups, 2 of 32, 4 of 9, 4 of 10, and 1 of 15 studies included deaths that occurred before starting treatment as early death or TRM for pediatric ALL, pediatric AML, pediatric TRM, and adult/pediatric APL studies, respectively. Seven studies explicitly excluded deaths that occurred before starting treatment in the analysis. Between 6.7% and 30.0% of studies reported first event deaths occurring after completion of treatment. The number of studies in which the authors reported deaths as a first event after HSCT varied and ranged from 0% to 70.0%. Some studies used deaths during induction or remission to define TRM, whereas others used deaths occurring at a set number of days to delineate TRM. Within therapeutic pediatric ALL studies, only 3.1% of studies used time from treatment to delineate TRM, whereas 44.4% of pediatric non-APL AML studies, 30.0% of pediatric TRM studies, and 46.7% of adult/pediatric APL studies used time from treatment initiation to delineate whether mortality was an early death or TRM. For example, in pediatric AML studies, 6 weeks was a common time frame used to delineate a death as early or treatment-related. In contrast, 8 days was a common time frame used to delineate an early death in APL. However, supplemental Tables 2 through 4 also demonstrates that this time frame varied within pediatric AML and adult/pediatric APL populations.

We have shown that many studies, particularly pediatric therapeutic ALL studies, do not provide a definition of TRM. Therapeutic studies do not generally present the overall toxic death rate over

the course of treatment, which is probably one of the more clinically meaningful estimates for families and healthcare professionals. There is a greater degree of variability whether deaths before starting treatment, after completion of treatment, or those that occur after HSCT are considered TRM. Although most therapeutic studies of pediatric ALL use induction and remission periods to delineate TRM, many studies in pediatric AML and adult/pediatric APL use a time frame from starting treatment to define early death or TRM, but this time period is not consistent across studies. Such variability highly influences a study's reported TRM rate, and thus, published TRM rates are not comparable and are difficult to interpret.

Inconsistency in defining attribution for cause of death

A second major impediment to adequate understanding of TRM is the issue of attribution, such as death because of infection, hemorrhage, tumor lysis syndrome, or organ dysfunction. There are 2 major problems with attribution. First, a reliable system of attribution related to TRM has never been developed. For example, infection-related mortality has been differently defined. Some authors have classified death in the presence of any fever as infection-related mortality, whereas others have required the presence of clinical or microbiologic documented infection for infection-related mortality.[6,7] Similarly, there are no definitions for what type or extent of hemorrhage constitutes bleeding-related death. Second, not uncommonly, patients will have multiple events close to death, such as organ dysfunction, infection, and hemorrhage. Currently, there are no clear ways to classify the primary cause of death for these patients. We have previously argued that attribution may never be possible because of multiple concurrent serious events proximal to death[8] and that, a system to identify certainty of attribution as well as important adverse events proximal to death would be useful.

Applicability to other malignancies

Although this overview focused on pediatric acute leukemia and adult/pediatric APL trials, similar issues are expected to occur in adult ALL and adult non-APL AML trials. Furthermore, there are expected to be additional challenges with adult and geriatric populations, particularly with deaths that occur after completion of therapy. Adults and elderly patients are expected to have some underlying rate of death from causes such as cardiovascular and pulmonary disease, which may or may not be compounded by cancer and anticancer therapy. How those deaths are classified, particularly with long-term follow-up, is challenging. Outside of ALL and AML, similar issues are expected in other hematologic malignancies treated with toxic therapies such as multiple myeloma and high grade lymphoma. Low-grade malignancies pose unique challenges; the delineation of TRM on the basis of remission status likely does not make sense in this setting.

Recommendations

Epidemiologic investigation into TRM characteristics and risk factors has been crippled by the absence of a standard definition for TRM. Furthermore, this deficit has impeded the valid comparison of TRM rates between different trials and over time. We suggest that further work in this area should be a priority. We suggest that all leukemia studies should be explicit about defining TRM with respect to whether deaths off treatment and following HSCT (if applicable) are included. Definitions are more heterogeneous in pediatric AML and considering that TRM is a major contributor to mortality in this disease, consistent definitions that either rely on induction/remission status or a consistent time frame should be established. Thus, paradigms for how to classify TRM in pediatric AML are urgently needed. The same considerations also apply to adult and pediatric APL trials. Consistent definitions would allow for meaningful interpretation of TRM rates across trials and would suggest where supportive care interventions are needed.

An optimal TRM classification system should be developed that can be reliably used across different abstractors, institutions, protocols, and countries. Furthermore, an optimal system must be feasible and easy to use. One possible approach could be to first identify elements required to determine whether a death is because of treatment or disease. For example, such elements would invariably include dates of death, diagnosis, start of treatment, end of treatment, and last relapse, and disease status. Then, with the use of these elements, an algorithm could be developed to classify whether the death is attributable to treatment. For example, a death in the setting of a patient who has started treatment, not yet ended treatment, is in remission, and has not relapsed would likely be classified as TRM across all diagnoses. An ideal algorithm would be useable across diagnoses and would be adaptable to circumstances such as relapse. For example, children who have relapsed but die of a fulminant infection could be differentially classified as TRM depending on the purpose of the analysis.

Although any proposal would need to be vetted through a group with diverse representation, 1 proposal for a TRM definition could be as follows. Deaths before treatment initiation are controversial. Some would argue that these deaths should be considered TRM because these deaths may be preventable through improved supportive care. However, others may argue that deaths because of hyperleukocytosis, which may occur before treatment initiation, should be considered related to disease. We agree that there are different perspectives but believe that it is important that hyperleukocytosis-related deaths be similarly classified irrespective of whether treatment was started. Whether these should be classified as treatment-related or disease-related is more difficult; classifying these as TRM would allow more homogeneity in classification because hyperleukocytosis is commonly associated with bleeding and sometimes it is not known whether hemorrhage is primarily driven by leukostasis or a bleeding diathesis.

Nonetheless, we emphasize that any TRM definition would need to be vetted through, and agreed on, by a diverse group with wide representation who would take these factors into account in their deliberations. Inclusion of hyperleukoctyosis deaths as TRM would increase reported TRM rates but this should not be problematic as long as TRM definitions were clear. Another suggestion for a TRM definition would be that in all studies of acute leukemia, induction TRM would be considered any death during the first intensive cycle of chemotherapy, even in protocols that use 2 cycles of induction. After the first cycle of chemotherapy, any death in morphologic remission would be considered TRM. In patients who do not remit after the first cycle of chemotherapy, TRM could be defined as any death not because of progressive disease although how to deal with this group of patients is more problematic. Finally, it is probably reasonable to set a maximum period of time after chemotherapy completion in which a remission

death is considered TRM. It is important to not solely use causation to define TRM because even motor vehicle accidents and suicide could in theory be related to the disease and treatment via central nervous system ischemia/hemorrhage and cognitive or psychologic effects. The choice of time period would need to balance the chance of mortality from natural causes versus death related to late effects of cancer therapy.

In addition, attribution for cause of death is a major issue that has not been addressed in leukemia. One solution could be to develop a system to categorize certainty of attribution (for example, definite, probable or possible hemorrhage as the cause of death). The issue of multiple causes of death has not been adequately explored in the pediatric or adult context. We suggest that all possible causes of death be listed along with the associated certainty of attribution.

Finally, these problems are equally important in pediatric and adult leukemia. We suggest that early collaboration between pediatric and adult hematologists is required to harmonize TRM definitions as much as possible to allow valid comparisons between pediatric and adult trials.

Conclusions

Clinical trials in acute leukemia commonly do not present definitions of TRM, and there is great variation across studies regarding which deaths are considered disease-related versus treatment-related. Consensus toward common definitions of TRM and methods to consistently approach attribution of TRM are critically important future goals. Collaboration between pediatric and adult hematologists will be crucial to permit comparisons across studies.

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Authorship

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