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Review Article

Differentiation Syndrome and Early Mortality in Patients with Acute Promyelocytic Leukemia (APL) Treated with All-Trans Retinoic Acid

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Summary

Acute promyelocytic leukaemia went from the most rapidly fatal form of leukaemia to the most curable within a decade, and the drug responsible brought its own lethal complication with it. Differentiation syndrome and early haemorrhagic death together account for almost all the mortality that remains in a disease with long-term survival above 80 per cent.

Objectives: To review the published evidence on differentiation syndrome and early mortality in acute promyelocytic leukaemia treated with all-trans retinoic acid: how often each occurs, which patients are at risk, what corticosteroid prophylaxis achieves, and why reported figures vary so widely.

Material and Methods: Narrative review of cooperative group trials, registry analyses, single-centre cohorts and expert recommendations indexed in PubMed and the major haematology journals. Studies were eligible if they reported the incidence, risk factors or outcome of differentiation syndrome, or early mortality, in a defined population with acute promyelocytic leukaemia. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Reported incidence of differentiation syndrome ranges from 17.8 to 62.4 per cent across cohorts, with around 25 to 30 per cent in the largest adult series. In 739 patients treated on two consecutive cooperative group protocols, severe but not moderate syndrome increased mortality, incidence was bimodal with peaks in the first and third weeks of therapy, and a white cell count above $5 \times 10^9/L$ together with an abnormal serum creatinine predicted severe disease. Corticosteroid prophylaxis reduced the odds of differentiation syndrome by roughly ninety per cent (OR 0.10, 95% CI 0.03-0.35). Early death remains the dominant residual problem: a registry analysis of 1,400 patients reported 17.3 per cent, rising with age, against 13.5 per cent in a trial-treated cohort. A peak white cell count above $43 \times 10^9/L$ predicted both early death and differentiation syndrome better than the count at diagnosis, including among patients classified as low risk.

Conclusion: The count that matters is the peak reached during induction rather than the one measured at diagnosis, which means risk stratification performed once at presentation misses patients who declare themselves over the following week. Corticosteroid prophylaxis is the intervention with the clearest effect and remains inconsistently applied.

Abbreviations: APL – Acute Promyelocytic Leukaemia, ATRA – All-Trans Retinoic Acid, ATO – Arsenic Trioxide, DS – Differentiation Syndrome, PML-RARA – Promyelocytic Leukaemia-Retinoic Acid Receptor Alpha, WBC – White Blood Cell Count, WBCdx – White Cell Count at Diagnosis, WBCmax – Peak White Cell Count, DIC – Disseminated Intravascular Coagulation, ICH – Intracranial Haemorrhage, CR – Complete Remission, OR – Odds Ratio.

Keywords: Acute Promyelocytic Leukaemia; Differentiation Syndrome; All-Trans Retinoic Acid; Early Death; Corticosteroid Prophylaxis

Introduction

Acute promyelocytic leukaemia is defined by the t(15;17) translocation and the resulting PML-RARA fusion, and it was for many years the most rapidly fatal form of leukaemia, with most patients dying of intractable haemorrhage before treatment could take effect [1,2]. The introduction of all-trans retinoic acid changed that within a decade, converting a disease described as uniformly lethal into the most curable of the acute myeloid leukaemias [3,4,5].

The drug works by inducing terminal differentiation of the malignant promyelocytes rather than killing them, and that mechanism produces its characteristic toxicity. Differentiation syndrome, originally described as the retinoic acid syndrome, presents with fever, respiratory distress, pulmonary infiltrates, weight gain, hypotension and renal impairment as the maturing cells accumulate and release inflammatory mediators [6,7,8].

Two problems therefore remain in a disease that is otherwise curable in more than four cases in five. The first is differentiation syndrome itself, which is treatable if recognised early and lethal if not [9]. The second is early death, predominantly haemorrhagic, occurring before or during the first days of therapy, and this has proved considerably more common outside clinical trials than within them [10,11].

This review sets out how often each occurs, which patients are at risk, what prophylaxis achieves, and why published incidence figures differ by more than threefold between comparable cohorts.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of differentiation syndrome and early mortality in acute promyelocytic leukaemia. Search terms combined acute promyelocytic leukaemia with differentiation syndrome, retinoic acid syndrome, all-trans retinoic acid, arsenic trioxide, early death, hyperleukocytosis and corticosteroid prophylaxis. Reference lists of retrieved trials and expert recommendations were screened by hand.

Eligibility: Studies were included if they reported the incidence, risk factors, severity grading or outcome of differentiation syndrome, or early mortality, in a defined population with acute promyelocytic leukaemia. Paediatric cohorts are included and identified as such. Historical series predating routine molecular confirmation are cited where they establish the natural history.

Data extraction and handling: Design, cohort size, induction regimen, definition of differentiation syndrome, prophylaxis policy and reported incidence or mortality were extracted as published. The definition applied is noted alongside every incidence figure, because diagnostic criteria for this syndrome are clinical and differ between series. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How often differentiation syndrome occurs: Reported incidence varies more than threefold. A Japanese cohort of 259 patients treated with retinoic acid and idarubicin reported an eight-week cumulative incidence of 17.8 per cent [11]. A retrospective series of 316 adults

treated with retinoic acid, arsenic trioxide or both reported 30.4 per cent [12]. A cohort of 86 newly diagnosed patients reported 62.4 per cent, split into 36.5 per cent mild and 25.9 per cent severe [13]. In paediatric patients receiving retinoic acid with arsenic trioxide the figure was 40.9 per cent (Figure 1) [14].

That spread reflects definition as much as biology. Differentiation syndrome is diagnosed clinically on a constellation of signs, and studies differ in how many features are required, whether mild cases are counted, and whether the syndrome is attributed when an alternative explanation such as sepsis is plausible [7,8,15]. A figure quoted without its diagnostic criteria is difficult to interpret.

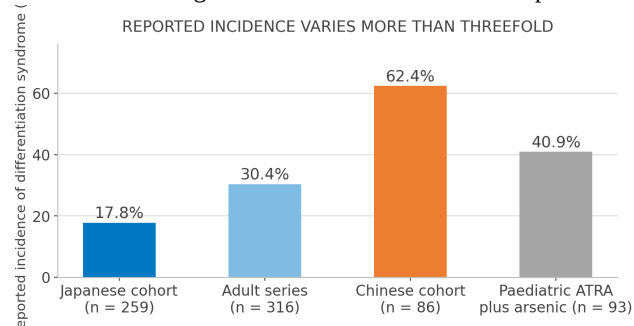


Figure 1: Reported incidence of differentiation syndrome across four cohorts [11,12,13,14]

Severity is what determines outcome: The most detailed characterisation comes from 739 patients enrolled in two consecutive cooperative group studies using retinoic acid with idarubicin. Severe but not moderate differentiation syndrome was associated with an increase in mortality, which is the finding that justifies grading the syndrome rather than treating it as a binary event [9].

Two further observations from that series shape practice. Incidence was bimodal, with peaks in the first and third weeks after starting retinoic acid, so a patient who passes the first week without event is not yet past the risk. And multivariate analysis identified a white cell count above $5 \times 10^9/L$ and an abnormal serum creatinine as correlating with severe disease [9]. Other groups have added body mass index [16] and a range of clinical and laboratory predictors [17] to that list, while interleukin 8 was examined and found not to be predictive [18].

Study	n	Regimen	Principal reported finding
Frankel et al. 1992 [6]	—	ATRA	Retinoic acid syndrome first described
Frankel et al. 1994 [7]	—	ATRA	New York study; syndrome characterised clinically
Montesinos et al. 2009 [9]	739	ATRA + IDA	Severe but not moderate syndrome raises mortality
Lo-Coco et al. 2013 [19]	Randomised	ATRA + ATO	Arsenic-based therapy superior in non-high-risk disease
Japanese cohort 2019 [11]	259	ATRA + IDA	Peak white cell count predicts both endpoints
Adult series 2025 [12]	316	ATRA and/or ATO	Prophylaxis reduces odds of syndrome by 90%

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

What corticosteroid prophylaxis achieves: Among 316 adults, 11.5 per cent of those who developed differentiation syndrome had received prophylactic corticosteroids during induction, against 35.5 per cent of those who did not develop it (Figure 2). On multivariable analysis, absence of prophylaxis was one of three independent predictors, with an odds ratio of 0.10 (95% CI 0.03-0.35) for the protective effect, alongside elevated peak white cell count (OR 1.07, 95% CI 1.03-1.11) and lower baseline serum albumin (OR 0.86, 95% CI 0.79-0.93) [12].

A roughly ninety per cent reduction in odds is a large effect for a cheap and widely available intervention, and it is consistent with the earlier cooperative group experience, in which systematic prednisone prophylaxis was associated with reduced incidence of severe disease [9,12]. Expert recommendations advise prophylaxis for high-risk patients, particularly those with elevated baseline counts or receiving combined retinoic acid and arsenic therapy [20].

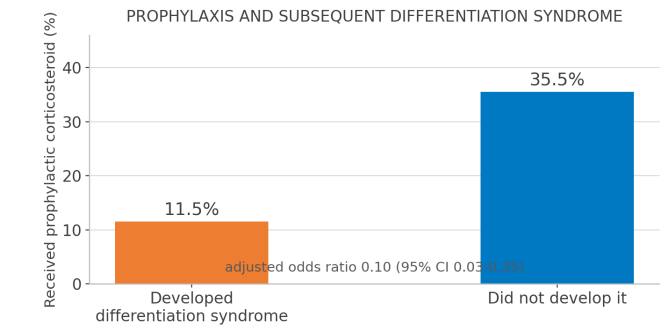


Figure 2: Prophylactic corticosteroid use among patients who did and did not develop differentiation syndrome [12]

The peak count matters more than the count at diagnosis: Risk stratification in this disease conventionally rests on the white cell count at presentation, with above $10 \times 10^9/L$ defining high risk [21]. Analysis of 259 patients tested whether the peak count reached during induction performed better, and found that it did. The eight-week cumulative incidence of early death was 13.5 per cent and of differentiation syndrome 17.8 per cent overall [11].

Among patients whose count at diagnosis was below $10 \times 10^9/L$, and who would therefore be classified as low or intermediate risk, a peak count above $43 \times 10^9/L$ was associated with early death in 26.7 per cent and differentiation syndrome in 40.0 per cent (Figure 3). Multivariate analysis confirmed the peak count as significantly associated with both endpoints [11]. A separate cohort found a peak count of $16 \times 10^9/L$ or more to be an independent risk factor for differentiation syndrome (OR 11.0, 95% CI 2.83-42.76) [13].

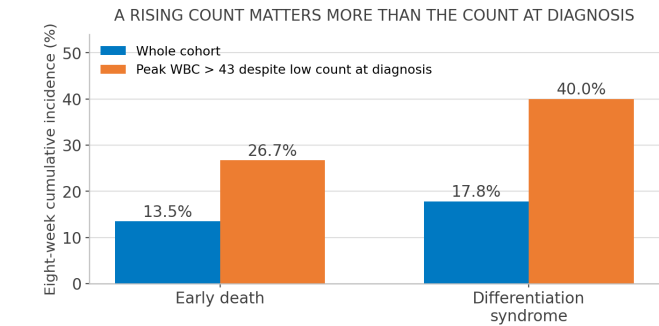


Figure 3: Outcomes by white cell trajectory, including patients low risk at diagnosis [11]

Early death remains the residual problem: A registry analysis of 1,400 patients reported an early death rate of 17.3 per cent, higher than trial-based reports and rising with age, particularly above 55 years (Figure 4) [11]. The trial-treated Japanese cohort recorded 13.5 per cent over eight weeks [11]. Death is caused predominantly by haemorrhage, with sepsis and differentiation syndrome accounting for most of the remainder [11,22].

The gap between registry and trial figures is the clinically important one. It reflects patients who die before diagnosis is confirmed, before retinoic acid is started, or before referral to a centre familiar with the disease, and none of those failures is addressed by improving the regimen. Expert guidance accordingly recommends starting retinoic acid on clinical suspicion rather than waiting for molecular confirmation, alongside aggressive blood product support [20,23].

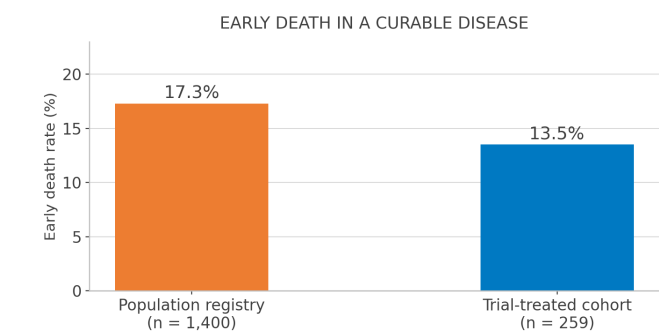


Figure 4: Early death rate in a population registry against a trial-treated cohort [11]

Risk factor	Reported effect	Source
WBC > 5 x 10 ⁹ /L at diagnosis	Predicts severe syndrome	739 patients [9]
Abnormal serum creatinine	Predicts severe syndrome	739 patients [9]
Peak WBC > 43 x 10 ⁹ /L	Early death 26.7%, syndrome 40.0%	259 patients [11]
Peak WBC ≥ 16 x 10 ⁹ /L	Odds ratio 11.0 for syndrome	86 patients [13]
No corticosteroid prophylaxis	Odds ratio 0.10 for protection	316 patients [12]
Low serum albumin	Odds ratio 0.86 per unit	316 patients [12]

Table 2: Reported independent risk factors for differentiation syndrome and early death

How the treatment landscape changed the question: Combined retinoic acid and arsenic trioxide replaced anthracycline-based induction for non-high-risk disease on the strength of randomised comparison [19,24], and arsenic had earlier been shown effective in relapsed and then in newly diagnosed patients without retinoic acid or chemotherapy [25,26]. Molecular monitoring by quantitative polymerase chain reaction allows relapse to be predicted and pre-empted [27,28].

Predicting early death before it happens: Because early death concentrates in the first days, several groups have tried to identify the patients at risk on admission. A scoring system derived for de novo disease combined presenting variables into a risk estimate [34], and single-centre analysis has examined which factors most strongly associate with death in newly diagnosed patients [33]. High-risk disease defined by presenting leucocytosis has been the subject of dedicated management recommendations [32].

The mechanistic work runs in parallel. In 86 newly diagnosed patients, white cell counts at diagnosis and on days 3 and 5 correlated moderately with tumour necrosis factor alpha at diagnosis, with coefficients between 0.609 and 0.648, while showing no

correlation with interleukin 6. The investigators proposed tumour necrosis factor alpha as a candidate marker for early death and identified a count above 7 x 10⁹/L on day 3 as marking higher risk [13].

Complication	Timing	Principal driver	Intervention
Haemorrhagic death	Days 0-10	Coagulopathy and DIC	Early ATRA and blood product support [20,23]
Differentiation syndrome	Weeks 1 and 3	Rising white cell count	Corticosteroid prophylaxis, cytoreduction [9,12]
Sepsis	Weeks 2-4	Neutropenia after cytoreduction	Standard neutropenic care [11,33]

Table 3: The three causes of early mortality, with characteristic timing and the intervention directed at each

Patients treated outside trials: Almost every figure quoted here comes from a cohort assembled for research. Outcomes among patients not enrolled in clinical trials have been examined separately and are consistently worse [35], which matches the registry and trial gap described above [11]. The difference is not attributable to the regimen, which is the same, but to how quickly the diagnosis is suspected and how familiar the treating team is with a disease most haematologists encounter only a handful of times.

Discussion

Two findings deserve to change practice and one explains why the literature looks inconsistent. The first is that the white cell count which predicts both differentiation syndrome and early death is the peak reached during induction, not the one measured at presentation [11,13]. Among patients whose diagnostic count placed them in the low-risk category, a peak above 43 x 10⁹/L carried a 26.7 per cent early death rate, which is worse than the average for the whole cohort [11].

The second is that corticosteroid prophylaxis reduces the odds of differentiation syndrome by around ninety per cent and is nonetheless given to only about a third of patients in a contemporary series [12]. For an intervention this cheap, with a complication this dangerous, that gap is difficult to justify on the published evidence.

Why the incidence figures disagree

An incidence range from 17.8 to 62.4 per cent across four cohorts cannot reflect biology alone [11,12,13,14]. Differentiation syndrome has no confirmatory test; it is diagnosed on a cluster of clinical features that overlap substantially with sepsis, fluid overload and pulmonary haemorrhage in a patient who is coagulopathic and neutropenic [7,8,29]. Whether mild cases are counted is the single largest source of variation, and the cohort reporting 62.4 per cent split its cases into 36.5 per cent mild and 25.9 per cent severe [13],

the latter figure sitting comfortably within the range others report overall.

The gap between trial and population outcomes

Early death at 17.3 per cent in a registry against 13.5 per cent in a trial cohort understates the difference, because registry series themselves capture only patients who reached diagnosis [11]. Patients who die of intracranial haemorrhage before the blood film is examined never enter either denominator.

Study limitations

The limitations belong to the underlying literature. Differentiation syndrome lacks an objective diagnostic standard, so incidence figures are not directly comparable between series [7,8,12,13]. The prophylaxis comparison is observational and prophylaxis was not randomly assigned, so confounding by indication cannot be excluded [12]. Cohorts differ in induction regimen, in whether cyto-reduction was used for hyperleukocytosis, and in transfusion thresholds, all of which affect both endpoints [11,19]. Registry analyses capture death reliably but attribute cause poorly [11]. And several formative series predate routine molecular confirmation, so historical incidence figures include patients who would now be classified differently [1,30,31].

Two gaps deserve naming. No randomised trial has compared corticosteroid prophylaxis against none, so the largest reported effect in this review rests on observational data [12]. And no study reviewed here reports whether monitoring the white cell trajectory and intervening on a rising count, rather than on the count at diagnosis, reduces either endpoint [11,13].

Conclusion

Differentiation syndrome affects somewhere between a fifth and a third of patients receiving all-trans retinoic acid, with the wide published range driven largely by whether mild cases are counted. Severe disease raises mortality and moderate disease does not, which makes severity grading essential rather than optional. The strongest predictors are a white cell count above $5 \times 10^9/L$ with abnormal creatinine at diagnosis, and more powerfully a peak count above $43 \times 10^9/L$ during induction, which identifies patients classified as low risk at presentation yet experiencing 26.7 per cent early death. Corticosteroid prophylaxis reduces the odds of the syndrome by roughly ninety per cent and reaches only a third of patients. Early death, still 17.3 per cent in registry data against a disease that is otherwise curable in more than four cases in five, remains the largest single opportunity in this disease, and it is addressed by starting treatment sooner rather than by treating differently.

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Every incidence figure quoted here was counted by somebody else, in cohorts assembled over three decades of cooperative group work.

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Conflict of Interest

No interest held by any author touches on the subject of this review.

Ethics Statement

Every study drawn on here was in the public record before the review was begun. It enrolled nobody, sampled nobody and opened no chart, so the question of ethical approval never arose.

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